as those intended for preventing, treating, or curing diseases or injuries "through specific immunization." The 1947 definition of products analogous to therapeutic serums excluded hormones. Hormones such as insulin and human growth hormone were licensed under the FDCA, not the PHSA. Despite the 1947 regulations, differentiating biologics from drugs remained challenging at the margins.

The advent of biotechnology, along with FDA organizational disputes, brought this issue to the forefront of the FDA's focus. In 1986, the FDA issued a policy statement stating that it would determine whether biotechnology products constituted biologics "based on the intended use of each product on a case-by-case basis." Thus, the FDA continued to make product-specific determinations informed by history and precedent, and different units of the FDA had to agree on the approval pathway for a given product. This proved to be difficult, with press reports of turf battles between the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) for jurisdiction over blockbuster biotechnology products and claims that the decisions were inconsistent. For example, epidermal growth factors were regulated as drugs because their first licensed indications were traditionally drugged indications. Most mAbs were licensed as biologics because of their biological source material and immunologic function. Recombinant insulin and human growth hormone, similar to their naturally derived counterparts, were licensed pursuant to NDAs. CDER and CBER subsequently executed an intercenter agreement (ICA) that attempted to clarify the governing authorities for products derived from living material. The agreement provided that the following products, among others, were subject to licensure under the PHSA: vaccines; proteins, peptides, and carbohydrates produced by cell culture (other than hormones and products previously derived from human or animal tissue and licensed as drugs); proteins made in transgenic animals; blood and blood products; and allergenic products. NDAs were required for, among other things, hormones (regardless of method of manufacture), synthetic mononucleotide and polynucleotide products, and naturally derived products other than vaccines or allergens. Twelve years later, the FDA consolidated a review of most therapeutic proteins in CDER, but this transfer did not modify the governing statutory scheme for any ICA product, and the FDA continued to decide whether new products were biological products or nonbiologic drugs on a case-by-case basis using the principles of the ICA and the historical precedent.

In February 2012, the FDA issued a draft guidance aimed at implementing recent legislation that added "protein (except any chemically synthesized polypeptide)" to the biological product definition. In this draft guidance, the FDA proposed a bright-line rule distinguishing protein from "peptides" and "chemically synthesized polypeptide[s]" that the FDA proposes to approve under the FDCA. The FDA proposed to define *protein* as "any alpha amino acid polymer with a specifically defined sequence that is greater than 40 amino acids in size." According to the draft guidance,