and/or polypeptides, maintenance of molecular conformation, and, hence, of biological activity, is dependent on noncovalent and covalent forces. The products are particularly sensitive to environmental factors, such as temperature changes, oxidation, light, ionic content, and shear. To ensure the maintenance of biological activity and to avoid degradation, stringent conditions for their storage are usually necessary.

The evaluation of stability may necessitate complex analytical methodologies. Assays for biological activity, where applicable, should be part of the pivotal stability studies. Appropriate physicochemical, biochemical, and immunochemical methods for the analysis of the molecular entity and the quantitative detection of degradation products should also be part of the stability program, whenever purity and molecular characteristics of the product permit use of these methodologies.

With these concerns in mind, the applicant should develop the proper supporting stability data for a biotechnological/biological product and consider many external conditions that can affect the product's potency, purity, and quality. Primary data to support a requested storage period for either drug substance (DS) or drug product (DP) should be based on long-term, real-time, real-condition stability studies. Thus, the development of a proper long-term stability program becomes critical to the successful development of a commercial product. The purpose of this document is to give guidance to applicants regarding the type of stability studies that need to be provided in support of marketing applications. It is understood that during the review and evaluation process, continuing updates of initial stability data may occur.

Where bulk material is to be stored after manufacture but before formulation and final manufacturing, stability data are provided on at least three batches for which manufacture and storage are representative of the manufacturing scale of production. A minimum of 6-month stability data at the time of submission should be submitted in cases where storage periods greater than 6 months are requested. For DS with storage periods of less than 6 months, the minimum amount of stability data in the initial submission should be determined on a case-by-case basis. Data from pilot plant scale batches of DS produced at a reduced scale of fermentation and purification may be provided at the time the dossier is submitted to the regulatory agencies, with a commitment to place the first three manufacturing scale batches into the long-term stability program after approval.

The quality of the batches of DS placed into the stability program is representative of the quality of the material used in the preclinical and clinical studies and of the quality of the material to be made at the manufacturing scale. In addition, the DS (bulk material) made at pilot plant scale should be produced by a process and stored under conditions representative of that used for the manufacturing scale. The DS entered into the stability program should be stored in containers that properly represent the actual holding containers used during manufacture. Containers of reduced size may be acceptable for DS stability testing, provided that they are constructed of the same material and use the same type of container/closure system that is intended to be used during manufacture.

During manufacture of biotechnological/biological products, the quality and control of certain intermediates may be critical to the production of the final product. In general, the manufacturer should identify intermediates and generate in-house data and process limits that assure their stability within the bounds of the developed process. Although the use of pilot plant scale data is permissible, the manufacturer should establish the suitability of such data by using the manufacturing scale process.