Formulation of proteins and monoclonal antibodies (mAbs)

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As discussed previously in Chapter 1, formulation to attain stability is only one area for successful pharmaceutical development. It is not necessary to provide a formulation that provides the best stability, but rather only one that meets the overall requirements for the target product profile. In this chapter, we will discuss the overall approaches used for development of formulations for protein therapeutics as well as the challenges and issues that occur during development. Previously the different degradation routes that proteins undergo were reviewed. Essentially the diversity of chemistry due to the differences in the 20 common amino acids that make up a protein results in challenges in determining the optimal conditions whereby the different degradation routes are all minimized. In addition to the chemical degradations, physical degradation routes involving conformational changes and aggregation also need to be addressed. This greater complexity of instability differentiates protein drugs from the more traditional small-molecule drugs.

Formulation of monoclonal antibodies

As discussed previously in Chapter 3, a majority of monoclonal antibodies (mAbs) have been formulated for IV administration. A summary of formulations of 46 mAbs, Fc fusion, and Fab conjugates approved in the US is shown in Table 4.1. More than half of the formulations (29) are liquids and the remaining (19) solid dosage forms prepared by lyophilization.

Dosage form assessment—solid versus liquid dosage forms

The choice between a liquid and solid dosage form requires a careful assessment of the TPP, which uses several sources including marketing research, formulation, and process development. Liquid products are more convenient for the end user, and can ensure better patient compliance since reconstitution of the product is not required. In addition, dosing accuracy may be better than for a reconstituted solid dosage form since considerable error may occur on measurement of volume added for reconstitution. However, since many of the chemical degradation routes are hydrolytically driven, the liquid formulations are usually less stable than solid dosage forms, which may limit their shelf life and require special handling during manufacture, shipping, storage, and use. Although it may be possible to minimize those reactions that reduce activity or quality of the final product, it usually is more difficult to control the physical stability of liquid protein products since proteins and mAbs are inherently sensitive to exposure to surfaces in the liquid state and may denature or aggregate if not adequately protected or appropriately handled. Exposure to final manufacturing

Monoclonal Antibodies. http://dx.doi.org/10.1016/B978-0-08-100296-4.00004-X