Potency assays

Regulatory agencies require that the final formulated drug product be safe and efficacious when administered to patients over the recommended lifetime storage of the drug. Thus, an important part of a stability program is the demonstration that for the specific approved drug the drug maintains its activity over the intended shelf life. This assessment requires the development of biologically relevant assays. Many protein therapeutics are pleotropic and may be used for treatment of different diseases. As an example, human growth hormone (hGH) can be used to treat burn victims as well as hypopituitary children requiring hormone for natural growth. Thus it would not be correct to develop a biological assay that assesses healing in burn victims if the hGH is being developed for treatment of growth inhibition due to lack of the hormone.

Development of potency assays can be categorized as in vivo animal-based, ex vivo cell- or tissue-based, or in vitro analytical-based assays. These types of assays and the advantages and disadvantages of each are herein discussed.

In vivo animal based

When the mechanism of action is not fully understood the use of a whole animal model is the preferred assay for assessing potency. One issue with this approach is how equivalent is the animal biochemistry to that of humans. Correlating responses in the animal model with that in humans can mitigate some of this. These assays are often difficult because of the variability in animal responses as well as the expense and time needed to perform such assays. As an example, the weight gain assay for hGH (Marx, Simpson, & Evans, 1942) results in coefficient of variability as high as 30–50% even when more than 10 animals are used in the assay (Jones, 1993). Although measuring weight gain for longer treatment times may attain an increased precision, this is generally not possible since the animal has immune responses to the exposure of the foreign human protein.

Ex vivo cell or tissue based

Cell-based assays are greatly preferred over the animal-based models since greater precision may be attained and the expense and time for obtaining results may be reduced. However, the choice of cell line may be crucial in the type of response, and the mechanism of action needs to be better understood. As an example, elucidation of the molecular interactions of hGH with the hGH receptor (Devos, Ultsch, & Kossiakoff, 1992) suggests that generation of a cell line that expresses the hGH receptor and proliferates in response to exposure to hGH may be a suitable replacement for the whole animal bioassay. Alternative approaches may use specific animal tissue that is responding to exposure to the protein drug. In vitro assays for human relaxin have been developed where the whole animal mouse pubic symphysis assay (Ferraiolo, Cronin, Bakhit, Chesnut, & Lyon, 1989) has been replaced by a uterine smooth cell contractility assay (Norstrom, Bryman, Wiquist, Sahni, & Lindblom, 1984) and a histamine release assay from rat mast cells transfected with the alpha subunit of FcεRI (Lowe, Jardieu, Van Gorp, & Fei, 1995).