

the protein formulation even though it is intended only for a single-dose injection. This is a very controversial practice. Regulatory agencies worldwide object to this approach if, in their opinion, the use of APs in a single-dose injectable product is practiced in order to “cover up” for inadequate aseptic manufacturing practices and controls.

Many countries require PET be performed for routine stability protocols and for special stability studies. Also there may be requests from agencies to do PET on containers that have been used (i.e., penetrated; partial volume withdrawn) to demonstrate that the product can still kill microorganisms. In mid-1995, the Australian Drug Evaluation Committee (ADEC) passed resolutions that in light of safety concerns with contamination and cross-contamination, the use of injectable products in multi-dose packages is discouraged. In order to support the use of a multidose product and the shelf-life once a package has been reconstituted or opened for use, AP efficacy data are required for approval.

OSMOLALITY (TONICITY) AGENTS

Salts or nonelectrolytes (e.g., glycerin) are added to protein formulations in order to achieve an isotonic solution. Nonelectrolytes often are preferred over salts as tonicity adjusters because of the potential problems salts cause in precipitating proteins. Generally, solutions containing proteins administered IV, IM, or SC do not have to be precisely isotonic because of immediate effects from dilution by the blood. Intrathecal and epidural injections into the cerebrospinal fluid require very precise specifications for the product to be isotonic and at physiological pH. This is because extremes in osmolality and/or pH can damage or destroy cells and cerebrospinal cells cannot be reproduced or replaced.

SIMPLE EXERCISE

For each of these commercial sterile solution formulations, name the purpose of each excipient.

Nebcin® (Lilly)

Tobramycin 80 mg
Sodium bisulfite 5 mg
Disodium EDTA 0.1 mg
Phenol 5 mg

Valium Injection (Roche)

Diazepam 5 mg
Propylene glycol 40%
Ethanol 10%
Benzoic acid/Sodium benzoate 5%
Benzyl alcohol 1.5%

Nutropin AQ® (Genentech)

Somatropin 10 mg
Sodium chloride 17.4 mg
Phenol 5 mg
Polysorbate 20.4 mg
Sodium citrate 10 mM

Rebif® (Serono)

Interferon beta-1 a 44 mcg
Human albumin 4 mg
Mannitol 27.3 mg
Sodium acetate 0.4 mg

REFERENCES

1. Akers MJ, Vasudevan V, Stickelmeyer M. Protein dosage form development. In: Nail SL, Akers MJ, eds. Borchardt RT, series editor. Development and Manufacture of Protein Pharmaceuticals. Volume in series on Pharmaceutical Biotechnology. New York, NY: Plenum, 2002:47–127.