the type of container, it should be effectively sealed to prevent the enclosed medicine becoming contaminated with microorganisms or other contaminants during storage prior to use. Containers should therefore be airtight and also preferably tamper evident. The types of containers and closures will be discussed further below.

Endotoxins and pyrogens

As well as being sterile, parenteral preparations must be practically free from endotoxins and pyrogens. These substances are bacterial products that may be released from certain types of bacteria when they are alive, or after they die. They may therefore be present in sterile products as a by-product of the sterilization process which kills the bacteria during manufacture. When they are injected into a patient they can cause fever, and even shock if present in sufficient quantities. Therefore parenteral products must comply with the test for bacterial endotoxins or the test for pyrogens. For further information on endotoxins and pyrogens and on depyrogenation of containers equipment and raw materials see Chapter 16 and 17.

Particulates

The final general test with which certain parenteral products much comply is for particulate contamination. They must be free of visible particles and contain only very low numbers of sub-visible particles. This is of particular importance for medicines administered intravenously. Particles inadvertently injected with a medicine will travel through the venous system to the heart and from there to the lungs. In the lungs the vascular system narrows to a network of capillaries around each alveolus and any suspended particles may become entrapped at this point preventing blood from flowing, resulting in a pulmonary embolism.

Pharmacopoeias have standards for particulate matter in injections for intravenous use, for example the European Pharmacopeia (PhEur) has limits on the number of 10 and 25 μm particles per container of injectable product. The PhEur notes that these levels would not be appropriate for suspensions for injection. Suspensions for injection are meant to be administered by the intramuscular, intra-articular or subcutaneous routes of administration.

Obviously suspensions are not (supposed to be) injected intravenously for the reasons noted above, but when injected intramuscularly or subcutaneously or into a joint space, the suspended particles will dissolve slowly and provide a prolonged effect. This may be many hours in the case of subcutaneous insulin suspension, or perhaps many weeks for a steroid suspension injected into a joint. The required dissolution characteristics will to a great extent determine the size and nature of the solid drug particles (e.g. amorphous or crystalline).

Emulsions can be injected intravenously, but here the maximum droplet size will be linked to capillary diameter. The droplet size must be controlled and is usually less than 3 μm in diameter to prevent oil embolisms forming in the blood-stream. However there is evidence that certain oil droplets may deform to some extent, to pass through a capillary without occluding it, such that oil droplets slightly larger than the diameter of a capillary can be administered.

Category-specific requirements

Pharmacopoeias usually recognize several distinct categories of parenteral product. These are injections, infusions, concentrates for injection or infusion, powders for injection or infusion and gels for injection.

Injections

Injections can be sterile solutions, emulsions or suspensions. They are prepared by dissolving, emulsifying or suspending the drug substance (or substances), together with any required excipients, in water or non-aqueous liquid or a mixture of aqueous and non-aqueous vehicles. Solutions for injection are clear and free from visible particles. Emulsions for injection must not show any evidence of phase separation (creaming or cracking – see Chapter 27). Suspensions for injection may show sediment, but if they do this must be readily resuspended on shaking to give a suspension that is sufficiently stable to allow a uniform dose to be withdrawn from the container.

With regard to the resuspension of sedimented injections in practice, it is not usual for particle size to be tested in a quantitative manner on a routine basis prior to use. Indeed resuspended injections can be administered in patients' homes or at GP clinics where particle size determination apparatus is not available. Thus, it is the responsibility of the original formulator/manufacturer of the suspension to provide the necessary data to convince the regulatory