⟨381⟩ ELASTOMERIC CLOSURES FOR INJECTIONS

An elastomeric closure may be of synthetic or natural origin. It is generally a complex mixture of many ingredients. These include the basic polymer, fillers, accelerators, vulcanizing agents, and pigments. The properties of the elastomeric closure are dependent not only upon these ingredients, but also on the processing procedure, such as mixing, milling, dusting agents used, molding, and curing.

Factors such as cleansing procedures, contacting media, and conditions of storage may also affect the suitability of an elastomeric closure for a specific use. Evaluation of such factors should be made by appropriate additional specific tests to determine the suitability of an elastomeric closure for its intended use. Criteria for the selection of an elastomeric closure should also include a careful review of all the ingredients to assure that no known or suspected carcinogens, or other toxic substances are added.

Definition—An *elastomeric closure* is a packaging component that is, or may be, in direct contact with the drug.

Biological Test Procedures

Two stages of testing are indicated. The first stage is the performance of in vitro tests according to the procedures set forth in chapter ⟨87⟩, *Biological Reactivity Tests, In Vitro*. Materials that meet the requirements of the in vitro tests are not required to undergo further testing. Materials that do not meet the requirements of the in vitro tests are subjected to the second stage of testing which is the performance of in vivo tests, i.e., the *Systemic Injection Test* and *Intracutaneous Test*, according to the procedures set forth in chapter *Biological Reactivity Tests, In Vivo* ⟨88⟩.

Physicochemical Test Procedures

The following tests are designed to determine pertinent physicochemical extraction characteristics of elastomeric closures. Since the tests are based on the extraction of the elastomer, it is essential that the designated amount of surface area of sample be available. In each case, the specified surface area is available for extraction at the designated temperature. The test methods are devised to detect the majority of expected variations.

Extraction Solvents—

A: Purified Water.

B: Drug product vehicle (where applicable).

C: Isopropyl alcohol.

Apparatus—

Autoclave—Use an autoclave capable of maintaining a temperature of 121 ± 2°, equipped with a thermometer, a pressure gauge, and a rack adequate to accommodate the test containers above the water level.

Oven—Use an oven, preferably a forced-draft model, that will maintain an operating temperature of 105° ± 2°.

Reflux Apparatus—Use a suitable reflux apparatus having a capacity of about 500 mL.

Procedure—

Preparation of Sample—Place in a suitable extraction container a sufficient number of elastomeric closures to provide 100 cm^2 of exposed surface area. Add 300 mL of purified water to each container, cover with a suitable inverted beaker, and autoclave at 121 ± 2° for 30 minutes. [NOTE—Adjust so that the temperature rises rapidly, preferably within 2 to 5 minutes.] Decant, using a stainless steel screen to hold the closures in the containers. Rinse with 100 mL of purified water, gently swirl, and discard the rinsings. Repeat with a second 100-mL portion of purified water. Treat all *blank* containers in a similar manner.

Extracts (with use of *Extraction Solvent A*)—Place a properly prepared *sample*, having an exposed surface area of 100 cm^2, in a suitable container, and add 200 mL of purified water. Cover with a suitable inverted beaker, and extract by heating in an autoclave at 121° for 2 hours, allowing adequate time for the liquid within the

container to reach the extraction temperature. Allow the autoclave to cool rapidly, and cool to room temperature. Treat the *blank* container in a similar manner.

Extracts (with use of *Extraction Solvent B or C*)—Place a properly prepared *sample*, having an exposed surface area of 100 cm^2, in a suitable *Reflux Apparatus* containing 200 mL of *Extraction Solvent*, and reflux for 30 minutes. Treat the *blank* in a similar manner.

Turbidity—[NOTE—Use *Extracts* prepared with *Extraction Solvent A*, *B*, or *C*.] Agitate the container, and transfer a sufficient quantity of *Extract*, diluted with *Extraction Solvent*, if necessary, to a cell. Measure the turbidity in a suitable ratio turbidimeter (see *Spectrophotometry and Light-Scattering* ⟨851⟩) against fixed reproducible standards.* The turbidity is the difference between the values obtained for the blank and the sample expressed in Nephelometric Turbidity Units (NTU), an arbitrary linear numerical scale expressing a haze range from absolute clarity to the zone of turbidity.

Reducing Agents—[NOTE—Use *Extracts* prepared with *Extraction Solvent A*.] Agitate the container, transfer 50 mL of *sample* extract to a suitable container, and titrate with 0.01 N iodine VS, using 3 mL of starch TS as the indicator. Treat the *blank* extract in a similar manner. The difference between the *blank* and the *sample* titration is expressed in mL of 0.01 N iodine.

Heavy Metals ⟨231⟩**—**[NOTE—Use *Extracts* prepared with *Extraction Solvent A* or *B*.] Transfer 20 mL of the *blank* and the *sample* extracts to separate color-comparison tubes. Transfer 2, 6, and 10 mL of *Standard Lead Solution* into separate color-comparison tubes, add 2 mL of 1 N acetic acid to each tube, and adjust the volume to 25 mL with purified water. Add 10 mL of freshly prepared hydrogen sulfide TS to each tube, mix, allow to stand for 5 minutes, and view downward over a white surface. Determine the amount of heavy metals in the *blank* and in the *sample*. The heavy metals content is the difference between the *blank* and the *sample*.

pH Change—[NOTE—Use *Extracts* prepared with *Extraction Solvent A* or *B*, adding to *extracts* obtained with *Solvent A* sufficient potassium chloride to provide a concentration of 0.1%.] Determine the pH of *sample* extracts *A* and *B* potentiometrically, performing blank determinations with *blank* extracts *A* and *B*, and making any necessary corrections. The pH change is the difference between the *blank* and the *sample*.

Total Extractables—[NOTE—Use *Extracts* prepared with *Extraction Solvent A*, *B*, or *C*.] Agitate the containers, and transfer 100-mL aliquots of the *blank* and the *sample* to separate, tared evaporating dishes. Evaporate on a steam bath to dryness (*Extracts* prepared with *Extraction Solvent C*) or in an oven at 100°, dry at 105° for 1 hour, cool in a desiccator, and weigh. Calculate the total extractables, in mg, by the formula:

$$2(W_U - W_B)$$

in which W_U is the weight, in mg, of residue found in the sample extract aliquot; and W_B is the weight, in mg, of residue found in the blank solution aliquot.