Good sterile technique is used during the filling, handling and surgical implantation of ALZET pumps. (Refer to Section VI for filling procedure and Section V for implantation procedure). ALZET pumps have been exposed to a sterilizing dose of radiation from a 60Co source.

When the environment in which the pump is to be used differs significantly from nominal osmotic body temperature (37°C) and osmolality (310 milliosmols/l), the pumping rate of ALZET pumps will be affected. (To calculate the pumping rate under specific temperature and osmolality conditions, refer to the equation in Section VI).  

ALZET Osmotic Pumps, Model 2ML4, should be removed upon completion of their delivery duration or by day 42 after implantation. After this time, drug delivery cannot be stopped immediately, are working with a viscous solution, or if you wish to attach a catheter, incise the pre-filled pump in sterile saline at 37°C for at least 4 to 6 hours (preferably overnight). (Refer to Section VI for details & for complete instructions).

When the environment in which the pump is to be used differs significantly from nominal osmotic body temperature (37°C) and osmolality (310 milliosmols/l), the pumping rate of ALZET pumps will be affected. (To calculate the pumping rate under specific temperature and osmolality conditions, refer to the equation in Section VI).

ALZET Osmotic Pumps, Model 2ML4, should be removed upon completion of their delivery duration or by day 42 after implantation. This experiment was performed with ALZET pumps. (To calculate the pumping rate under specific temperature and osmolality conditions, refer to the equation in Section VI).

ALZET Osmotic Pumps, Model 2ML4, should be removed upon completion of their delivery duration or by day 42 after implantation. After this time, drug delivery cannot be stopped immediately, are working with a viscous solution, or if you wish to attach a catheter, incise the pre-filled pump in sterile saline at 37°C for at least 4 to 6 hours (preferably overnight). (Refer to Section VI for details & for complete instructions).

A. Complete Osmotic Pump System with Flow Moderator In Place

1. Nominal Performance (at 37°C)
   - Pumping Rate: 2.5 µl/hr
   - Duration: 28 days
   - Reservoir Volume: 2000 µl (2 ml)

   The nominal performance is a target for all pumps manufactured. Individual lots of pumps may vary from this target within limits. The actual pumping rate and fill volume of this particular lot (derived by statistical testing) are listed with the lot specifications at the top of this instruction sheet. Always use actual pumping rate and fill volume information specific to each lot of pumps when making dose calculations.

2. Dimensions, overall
   - Diameter: 1.4 cm
   - Weight (empty): 5.1 g
   - Total Displaced Volume: 6.5 ml

3. B. Components
   - 1. Filling Tube
      - Length (tube only): 3.8 cm
      - Diameter (tube): 25 µm
      - O.D. (tube): 0.05 cm
      - I.D. (tube): 0.03 cm
   - 2. Flow Moderator
      - Length (overall): 4.6 cm
      - Gauge (tube): 21
      - O.D. (tube): 0.08 cm
      - I.D. (tube): 0.05 cm
   - Weight: 0.9 g
      - Material (cap): polyethylene
      - Material (flush needle): stainless steel
      - Material (tube): stainless steel

4. Pump Body Materials
   - Outer Membrane: cellulose ester blend
   - Drug Reservoir: thermoplastic hydrocarbon elastomer
   - Inner Membrane: cellulose ester blend

II. Checklist for Satisfactory Performance of the ALZET Osmotic Pump

1. Use the mean pumping rate and fill volume information specific to this lot of pumps when making dose calculations.

2. ALZET Osmotic pumps are not completely discharged ALZET pump cannot be refilled or re-used.

3. All ALZET pumps are completely filled and all fill volumes have been recorded. (Refer to Section III for filling technique.)

4. The vehicle-drug combination to be delivered is compatible with the interior of the ALZET® Osmotic Pump. (Refer to Section IV for vehicle compatibility guidelines).

5. The experiment drug to be delivered is soluble in the vehicle solution at 37°C for the duration of the experiment.

6. The drug to be delivered is stable in the vehicle solution at 37°C for the duration of the experiment.

7. The mass rate of drug dissolution is calculated using the following equation:

   \[ k = \frac{Q}{C} \]

   Here, \( k \) is the mass delivery rate (µg/hr), \( Q \) is the volume delivery rate (µl/hr) of the drug solution from the pump, and \( C \) is the concentration (µg/ml) of the agent in the vehicle.
V. Implementation of the ALZET Osmotic Pump In Vivo

The Model 2ML4 ALZET osmotic pump can be implanted subcutaneously in an animal that weighs at least 150 grams. For subcutaneous placement, a small incision is made in the skin between the scapulae. Using a hemostat, a small pocket is made for leaving the subcutaneous connective tissues apart. The pump is inserted into the pocket with the flow moderator pointing away from the incision to prevent air from being trapped. For intraperitoneal placement, make a small midline incision in the skin below the rib cage of an animal weighing at least 300 grams. Another small incision in the abdominal wall is made directly under the incision. The pump is inserted, flow moderator first, into the peritoneal cavity. The muscle incision is closed with Steri-Strips. The skin incision can be sutured or clips can be used. Be sure to remove the pump upon completion of the delivery duration (See Equations in Section II). This explanation data is calculated based on nominal duration. Refer to the equation in Section VI, part C, and the actual release rate and fill volume specifications to calculate the exact delivery duration and choose the appropriate ALZET osmotic pump for this date of your experiment.

For additional information about surgical procedures, contact ALZET Technical Support at 800-692-2990 U.S. and Canada. A video demonstrating several surgical implantation procedures is available at no charge.

VI. Operation of the ALZET Osmotic Pump

ALZET pumps are precision drug administration tools. This section details the actual release rate of medications from the osmotic pumps. It is critical to note that you received, and the method by which these figures were determined. After a start-up transient, the Model 2ML4 ALZET pumps deliver the drug solution at a constant rate within a predictable range all at but about 5% of the reservoir contents have been delivered; then the rate falls rapidly to zero.

The method DURECT uses to estimate the pumping rate of osmotic pumps is to measure its pumping rate in vitro in 0.9% saline at 37°C (± 0.5°C). This in vitro method gives a measure of regulation capacity - ovary is technical precision of drug delivery between pumps - and allows an estimate of the pumping rate to be expected inhomogenous body. The pumping capacity of saline is isotonic. For example, in rats and mice the pumping rate of subcutaneously or intraperitoneally implanted osmotic pumps is within 5% of the in vivo rate.

A. In Vitro Qualification Test

A random sample of 20 ALZET pumps is selected from the same lot as the product which you have received. These pumps are filled with a dye solution according to the manufacturer's specifications for the Mean Fill Volume, including standard deviation, appear in the lot specifications section on the other side of this instruction sheet.

After filling, each ALZET pump is submerged in 0.9% saline at 37°C (± 0.5°C). These pumps are transferred to test tubes containing fresh saline at regular intervals through day 28. The output of each pump is analyzed against a standard. Over the 6 to 672 hour time period, each pump operates at a constant rate for 28 days. Precision of rat saline, the coefficient of variation (CV) of dependent pumping rate is 10%, with a standard error of the mean of 5% (SEM). The variation in in vitro pumping rates among pumps on a given day and within 30% of the pumping rate over 28 days appears in the lot specifications on the other side of this instruction sheet.

B. Start-Up Time

If a pump is loaded at room temperature (23°C) with a solution also at room temperature, and then placed in isotonic saline at 37°C, the pumping rate will not reach steady state for several hours. If your experiment requires immediate pumping, DURECT suggests you place the prefilled pumps in 0.9% saline for at least 6 to 8 hours (preferably overnight) at 37°C before implantation. This procedure is necessary when the drug solution will be used with a catheter, or when viscous solutions are delivered; then the rate falls rapidly to zero.

C. Determination of Pumping Duration

The duration of pumping can be computed from the following equation.

\[ D = \frac{(V/Q) \cdot 0.95}{\pi - 0.007} \]

Here, \( D \) is the specified pumping rate of the pumps at 37°C in 0.9% saline (µl/hr), \( T \) is the ambient temperature (°C), and \( \pi \) is the osmotic pressure of the pump environment (atm).

The above formula is used in the range of \( x = 0 \) to 25 atm and \( T = 4°C \) to 42°C. At 42°C, the temperature effect is minimal. In actual applications, the pumping rate is typically 7.5 atm. The equation is predictive within ±10%. Environmental temperatures above 42°C have been found to cause fluctuating delivery rates and are not recommended. Please consult the manufacturer's specifications for the Model 2ML4. Note that as \( Q \) decreases in proportion to environmental temperature, the pumping duration increases.

D. Determination of Performance Outside Mammalian Ranges of Temperature and Osmolarity

The following equation can be used to predict the pumping rate in heterothermic and hypotonic environments.

\[ Q = \frac{Q_0}{\left[1 + \left(\frac{T}{T_0} - 1\right)^{n}\right]} \]

The duration of pumping can be computed from the following equation.

\[ D = \frac{V}{Q} \]

Where:

- \( Q \) = Rate of pumping (µl/hr)
- \( Q_0 \) = Rate of pumping at 37°C in 0.9% saline (µl/hr)
- \( T \) = Temperature of the environment (°C)
- \( T_0 \) = Temperature of saline (37°C)
- \( n \) = Temperature sensitivity

E. Analysis for the Concentration of Indicator in ALZET Osmotic Pump

To verify that experimental results are derived from continuous administration of the drug solution, perform the following steps:

1. Mix the contents of the test tube against a standard.
2. Repeat this step until the concentration of indicator in each test tube against a standard.
3. Remove the pump from the test tube.
4. Insert the pump into the pocket with the flow moderator pointing away from the incision to prevent air from being trapped.
5. The remaining solution from the pump reservoir.
6. The syringe attached to the distal part of the catheter.
7. Place the pump in sterile 0.9% saline at 37°C for 4 to 6 hours (preferably overnight). This will allow the pump to begin operating before implantation, and will minimize the chance of an occlusion or clot forming in the catheter. This step is necessary in all catheter applications. The pump and catheter can now be implanted.

VIII. Verifying the Accuracy of ALZET Osmotic Pumps

To verify that experimental results are derived from continuous administration of the pump solution, perform the following steps:

1. Mix the contents of the test tube against a standard.
2. Repeat this step until the concentration of indicator in each test tube against a standard.
3. Remove the pump from the test tube.
4. Insert the pump into the pocket with the flow moderator pointing away from the incision to prevent air from being trapped.
5. The remaining solution from the pump reservoir.
6. The syringe attached to the distal part of the catheter.
7. Place the pump in sterile 0.9% saline at 37°C for 4 to 6 hours (preferably overnight). This will allow the pump to begin operating before implantation, and will minimize the chance of an occlusion or clot forming in the catheter. This step is necessary in all catheter applications. The pump and catheter can now be implanted.

IX. Additional Technical Information About ALZET Osmotic Pumps

A wealth of information on ALZET osmotic pumps and their uses is available through ALZET Technical Support. Through this complimentary service you can request:

- A Technical Information Manual
- A video of commonly used surgical implantation procedures
- Custom searches of the ALZET osmotic pump bibliography publications
- Presentation materials for authors presenting their work
- Information about ALZET Brain Infusion Kits, ALZET Catheters and other products

To obtain any of these materials, or if you desire additional information, contact ALZET Technical Support at 800-692-2990 U.S. and Canada. A video demonstrating several surgical implantation procedures is available at no charge.

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