Good sterile technique is used during the filling, handling and surgical administration. The mass rate of drug infusion is calculated using the following equation:

\[ \text{ko} = Q \cdot Cd \]

where, \( ko \) is the mean infusion rate (\( \mu g/hr \)), \( Q \) is the volume delivery rate (\( l/hr \)) of the pump, and \( Cd \) is the concentration of drug in the pump. If back pressure is encountered, the filling tube can be cocked at a slight angle to allow the solution to expand and be wiped with an aqueous solution of 70% isopropanol immediately before use. It is essential that each pump is filled completely with solution and that correct filling is verified by the method described below. Air bubbles trapped in the pump reservoir or flow modulator can result in unpredictable pumping rate fluctuations. Solutions should be at room temperature during filling.

When the environment in which the pump is to be used differs significantly from normal mammalian 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 Vl, part C to calculate the exact delivery duration and maximum explantation date for this lot of osmotic pumps.

Via a catheter, ALZET pumps can be used to deliver substances into the venous or arterial circulation, into the brain, or into any organ, tumor, or body cavity. (For instructions on how to prepare the pump for these applications, refer to Section Vl.)

Correct operation of ALZET pumps is verified by monitoring blood levels of drug during the course of the experiment, by determining the residual amount of solution remaining in the pump at the end of the experiment, or by testing in vivo. (Refer to Section VII for a description of these verification techniques.)

### III. Instructions for Filling ALZET Osmotic Pumps

#### Section I

**A. Complete Osmotic Pump System with Flow Moderator In Place**

1. **Nominal Performance (at 37°C)**
   - **Pumping Rate:** 5.0 µl/h (± 0.75 µl/h)
   - **Duration:** 14 days
   - **Reservoir Volume:** 2000 µl (2.0 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.

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

3. **B. Components**
   - **Filling Tube**
     - **Length (tube only):** 3.5 cm
     - **Gauge (tube only):** 25
     - **O.D. (tube):** 0.05 cm
     - **I.D. (tube):** 0.03 cm

   - **Flow Moderator**
     - **Length (overall):** 4.6 cm
     - **Gauge (tube):** 21
     - **O.D. (tube):** 0.08 cm
     - **I.D. (tube):** 0.05 cm
     - **Material (cap):** polyethylene
     - **Material (flange):** styrene acrylonitrile
     - **Material (tube):** stainless steel

   - **3. Polymer Body Materials**
     - **Outer Membrane:** cellulose ester blend
     - **Drug Reservoir:** thermoplastic hydrocarbon elastomer

#### Section II

**I. Technical Description of the ALZET Osmotic Pump Model 2ML2**

- The mass rate of drug infusion is calculated using the following equation:

\[ \text{ko} = Q \cdot C_d \]

where, \( ko \) is the mass rate of drug delivery (µg/h), \( Q \) is the volume delivery rate (µl/h) of the solution from the pump, and \( C_d \) is the concentration (µg/ml) of the agent in the solution.

- Chemical compatibility is determined by the filling, handling and surgical implantation of osmotic pumps. (Refer to Section III for filling procedure and Section V for implantation procedure.) ALZET pumps have been exposed to a sterilizing dose of radiation from a 60Co source.

- The pumps are compatible with aqueous solutions, dilute acids and bases, dilute or low concentrations of DMSO and alcohol, and up to 100% propylene and polyethylene glycol. ALZET pumps are not compatible with alkali and acidic hydrocarbons, such as heptane, toluene, and natural oils. Contact with such substances can result in a pump malfunction. Table I provides examples of some commonly used solvents known to be compatible with the pump.

#### Section III

**A. Complete Osmotic Pump System with Flow Moderator In Place**

- The mean infusion rate of the pump is calculated using the following equation:

\[ \mu g/h = \frac{Q \cdot C_d}{\text{Volume delivered}} \]

where, \( \mu g/h \) is the mean infusion rate, \( Q \) is the volume delivery rate, and \( C_d \) is the concentration of drug in the solution.

- For the solution delivery rate of the ALZET pump, the volume delivery rate of the solution from the pump, and the concentration of the drug in the solution are critical factors.

- ALZET pumps are not compatible with alkali and acidic hydrocarbons, such as heptane, toluene, and natural oils. Contact with such substances can result in a pump malfunction. Table I provides examples of some commonly used solvents known to be compatible with the pump.

#### TABLE I

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Compatibility with ALZET Osmotic Pumps</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>Compatible</td>
</tr>
<tr>
<td>Ethanol</td>
<td>Compatible</td>
</tr>
<tr>
<td>Propylene glycol</td>
<td>Compatible</td>
</tr>
<tr>
<td>DMSO</td>
<td>Compatible</td>
</tr>
<tr>
<td>DMF</td>
<td>Compatible</td>
</tr>
<tr>
<td>DMF    15%</td>
<td>Compatible</td>
</tr>
<tr>
<td>DMSO</td>
<td>Compatible</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Compatible</td>
</tr>
<tr>
<td>Tween 80</td>
<td>Compatible</td>
</tr>
<tr>
<td>Solutol</td>
<td>Up to 30% in water</td>
</tr>
<tr>
<td>Ringer's solution</td>
<td>Compatible</td>
</tr>
<tr>
<td>Phosphate buffer</td>
<td>Compatible</td>
</tr>
<tr>
<td>Sodium chloride</td>
<td>Compatible</td>
</tr>
<tr>
<td>Glucose</td>
<td>Compatible</td>
</tr>
<tr>
<td>1-Methyl-2-Pyrrolidone</td>
<td>Compatible</td>
</tr>
<tr>
<td>Polyethylene glycol 300 or 400</td>
<td>Compatible</td>
</tr>
<tr>
<td>Polyethylene glycol, reagent</td>
<td>Compatible</td>
</tr>
</tbody>
</table>

**Acids, with pH greater than 1.8**

- Bases, with pH less than 14
- Cremophor EL, up to 25% in water
- Cetyltrimethyl ammonium bromide (bacterialicide)
- Cyclodextrin
- Dextrane, up to 5% in water or NaCl
- N,N-Dimethyl formamide (DMF), up to 25% in water
- DMSO, up to 50% in water or polyethylene glycol
- DMF, up to 50% in ethanol (e+15%) and water
- Ethanol, up to 15% in water

**Glycerol**

- 1-Methyl-2-Pyrrolidone, up to 12.5% in water
- Phosphate buffer
- Polyethylene glycol 300 or 400, reagent or in water
- Polyethylene glycol, reagent or in water
- Ringer's solution (with or without lactate)
- Saline, 0.9% (or other aqueous salt solution
- Solute for saline injection
- Solvent, up to 30% in water
- Tween 80, up to 2% in water
- Water, distilled

**Note:** The solvents listed above are known to be compatible with the reservoir material of the pump. Caution must be taken to ensure the chosen solvent is biocompatible with tissues and fluids at the site of administration.
If the solvent you wish to use is not listed in Table 1, an ALZAID test kit is available to allow you to assess agent and solvent compatibility with ALZET pumps. This test kit provides you with the necessary information to confirm compatibility with ALZET pumps. The test kit is available to allow you to assess agent and solvent compatibility. A wealth of information on ALZET osmotic pumps and their uses is available through ALZET Technical Information Services. Through this complimentary service you can request:

• A Technical Information Manual
• A list of ALZET pump products
• A wealth of information on ALZET osmotic pumps and their uses is available

VIII. Verifying the Accuracy of ALZET Osmotic Pumps

To verify that experimental results are derived from continuous administration of the drug solution, DIRECT recommends that ALZET pump users verify the drug delivery rates determined in vitro, such as through spectrophotometric analysis.

A. Determination of Average Pumping Rate

The reservoir volume of ALZET osmotic pumps is slightly larger than that required to achieve steady-state delivery. During this time, the volume decreases in proportion to the environmental temperature, duration increases. At normal mammalian osmolality of 310 milliosmols/l, the osmotic pressure (\(\pi\)) can be calculated as follows:

\[\pi = \frac{Q}{V} \cdot \frac{1}{t}\]

where \(Q\) is the specified pumping rate of the pumps at 37°C in 0.9% saline (µl/h), \(V\) is the reservoir volume (ml), and \(t\) is the time interval between transfers.

B. Determination of the In Vitro Pumping Rate

ALZET pumps are supplied with a specified volume pumping rate determined in isotonic saline at 37°C (± 0.5°C). In the event that the user finds it necessary to test the pumping rate, DIRECT recommends the following steps be taken:

Step 1. Prepare a solution of known concentration of an indicator dissolved in isotonic saline. The amount of indicator pumped out of the pump will be the basis for the pumping rate calculation. Therefore, the indicator solution should be compatible with the pump and be easy to analyze in isotonic saline. (One such indicator is FD&C Blue #1 dye, available from Bicton Colors, 5256 Baldwin St., St. Louis, MO 63143; stock no. 3536, or until all batch is used.)

Step 2. Fill the ALZET pump with the indicator solution according to Section II:

Step 3. Place the ALZET pump into a 10 ml test tube filled with 7 ml of isotonic saline and pre-incubated at 37°C (± 0.5°C). Cap the tube to prevent evaporation.

Step 4. Record the starting time of the incubation.

Step 5. Transfer the ALZET pump to a new test tube filled with 30 ml of isotonic saline approximately every 24 hours. Record the precise time of the transfer and/or the time interval between transfers.

Step 6. Repeat Step 5 for 14 days.

Step 7. Analyze the concentration of indicator in each test tube against a standard curve to determine the amount of indicator pumped during each interval time. From this amount and the concentration of the indicator in each test tube, the volume pumped through the pump can be calculated. Here Q is the microliters of solution delivered each interval during each experiment. Divide by the time interval in hours to obtain the hourly volume pumping rate. Note: When FD&C Blue #1 dye is used, the recommended wavelength for spectrophotometric analysis is 630 nm.

IX. Additional Technical Information About ALZET Osmotic Pumps

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DURECT Technical Support
DURECT Corporation
P.O. Box 530
Cupertino, CA 95015-0530

800-690-2990 (U.S.A. and Canada)
408-367-4036 (Outside the U.S.)
408-367-4030 (International)
direct@durect.com (e-mail)

www.alzet.com

X. Warranty

For a period of 12 months from date of shipment, DURECT warrants that the ALZET® Osmotic Pump (“Product”) is free from defects in materials and workmanship, and will, on average, deliver its contents at the rate and within the parameters specified in the lot specifications section on the product label. To verify that experimental results are derived from continuous administration of the drug solution, DIRECT recommends that ALZET pump users verify the drug delivery rates determined in vitro, such as through spectrophotometric analysis.

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