When the environment in which the pump is to be used differs significantly from its application environment, such as temperature or osmolality (310 milliosmols/l), the pumping rate of ALZET pumps will be affected. (% calculate the pumping rate under specific temperature and osmolality conditions, refer to the equation in Section VI.)

ALZET micro-osmotic pumps, Model 1007D, should be removed upon completion of the delivery duration by day 10 after implantation. After this time, due to the continued attraction of water into the pump, the drug solution will leak at a concentrated salt solution resulting in local irritation in the animal. (This explanation date is 10* after the pump is removed from an animal.) The equation in Section VI, Part C, calculate the exact delivery duration and maximum exact duration for each of the lot of micro-osmotic pumps.

When you receive the pump, it is recommended that the pump be placed into sterile saline at 37°C for at least 4 to 6 hours, or until the residual amount of solution remaining in the pump at the end of the experiment, or by day 10 after implantation.

If you desire the pump to start immediately, are working with a model pump which is pre-filled pump in sterile saline at 37°C for at least 4 to 6 hours, or until the residual amount of solution remaining in the pump at the end of the experiment, or by day 10 after implantation.

If back pressure is encountered, the filling tube can be cocked at a slight angle during the filling process. The volume of air being introduced can be reduced slightly by moving the filling tube back and forth, or by inserting and removing the flow moderator several times before inserting the filling tube.

If, after a second filling, the volume is less than 90% of the reservoir volume indicated on the lot specifications at the top of this instruction sheet, call ALZET Technical Information Services for assistance at 800-652-2390 (U.S. and Canada).

IV. Solvent and Agent Compatibility With ALZET Osmotic Pumps

The pumps are compatible with aqueous solutions, dilute acids and bases, dilute or low concentrations of DMSO and alcohol, and up to 15% of propylene glycol. ALZET pumps are not compatible with aliphatic and aromatic hydrocarbons, such as heptane, toluene, n-hexane, n-pentane, n-hexadecane, or any aromatic solvent which will adversely affect the pump malfunction. Table 1 provides examples of some commonly used solvents and their compatibility with ALZET Osmotic Pumps.

Note the following examples are provided to assist with the choice of compatible solvents, but are not to be considered a complete listing of biocompatible with waters and fluids at the site of administration.

### Table 1

<table>
<thead>
<tr>
<th>Compound/Concentration</th>
<th>Compatibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>Compatible</td>
</tr>
<tr>
<td>Distilled water</td>
<td>Compatible</td>
</tr>
<tr>
<td>Phosphate buffer</td>
<td>Compatible</td>
</tr>
<tr>
<td>Water, distilled</td>
<td>Compatible</td>
</tr>
<tr>
<td>Glycerol</td>
<td>Compatible</td>
</tr>
<tr>
<td>Solutol, up to 30% in water</td>
<td>Compatible</td>
</tr>
<tr>
<td>Saline, 0.9% (or other aqueous salt solution)</td>
<td>Compatible</td>
</tr>
<tr>
<td>Propylene glycol, neat or in water</td>
<td>Compatible</td>
</tr>
<tr>
<td>Dextrose, up to 5%, in water or NaCl</td>
<td>Compatible</td>
</tr>
<tr>
<td>Cremophor EL, up to 25% in water</td>
<td>Compatible</td>
</tr>
<tr>
<td>10% DMSO in 60% ethanol</td>
<td>Compatible</td>
</tr>
<tr>
<td>50% DMSO in 50% water</td>
<td>Compatible</td>
</tr>
<tr>
<td>Ethanol, up to 15% in water</td>
<td>Compatible</td>
</tr>
<tr>
<td>N,N-Dimethylformamide, up to 25% in water</td>
<td>Compatible</td>
</tr>
<tr>
<td>Isopropanol, up to 75% in water</td>
<td>Compatible</td>
</tr>
<tr>
<td>Isobutanol, up to 75% in water</td>
<td>Compatible</td>
</tr>
<tr>
<td>Methanol, up to 95% in water</td>
<td>Compatible</td>
</tr>
<tr>
<td>Acetonitrile, up to 95% in water</td>
<td>Compatible</td>
</tr>
<tr>
<td>DMF, up to 95% in ethanol or water</td>
<td>Compatible</td>
</tr>
<tr>
<td>Ethylene glycol</td>
<td>Compatible</td>
</tr>
<tr>
<td>Ethanol, up to 30% in water</td>
<td>Compatible</td>
</tr>
<tr>
<td>Methanol, up to 50% in water</td>
<td>Compatible</td>
</tr>
<tr>
<td>DMSO, up to 50% in water or ethanol</td>
<td>Compatible</td>
</tr>
<tr>
<td>Propylene glycol</td>
<td>Compatible</td>
</tr>
<tr>
<td>Acetone, up to 25% in water</td>
<td>Compatible</td>
</tr>
<tr>
<td>Isopropanol, up to 100% in water</td>
<td>Compatible</td>
</tr>
<tr>
<td>Methanol, up to 80% in water</td>
<td>Compatible</td>
</tr>
<tr>
<td>Ethanol, up to 75% in water</td>
<td>Compatible</td>
</tr>
<tr>
<td>Propylene glycol</td>
<td>Compatible</td>
</tr>
<tr>
<td>Acetonitrile, up to 95% in water</td>
<td>Compatible</td>
</tr>
<tr>
<td>DMF, up to 95% in water or ethanol</td>
<td>Compatible</td>
</tr>
</tbody>
</table>

Note: Listed are not all solvents that are compatible with the reservoir material of ALZET Osmotic pumps. Caution must be taken to also consider whether a solvent is biocompatible with tissues and fluids at the site of administration.
If the solution you wish to use is not listed in Table 1, an ALZAD® chemically compatible solvent can be used. This is indicated in the solvent and solvent compatibility with ALZET pumps. The test kit provides you with the necessary pump accessories, such as flow moderators for testing your agents and vehicles before use with osmotic pumps. DURECT strongly recommends the use of this test under the following circumstances:

1. When the solution you wish to use is not in Table 1.
2. When the agent is in its free base form.
3. When the agent is known to bind tenaciously to various polymeric materials.

To order an ALZET test kit, call 877-922-9338 (toll free in the U.S. and Canada).

A solution which generates gases within the pump during use makes the pumping rate highly unpredictable. Also, solutions with precipitated solids may lead to plugging of the osmotic pump. It is generally recommended that the pump should be room temperature when filling the pump.

All ALZET pumps deliver homogeneous viscous solutions with a viscosity of less than 100,000 centipoise. Suspensions may be used. If the viscosity of the pump is not reduced it should not be stored for the duration of delivery.

V. Operation of the ALZET Micro-Osmotic Pump in Vivo

The ALZET micro-osmotic pump can be implanted subcutaneously in an animal weighing at least 10 grams. After the incision and subcutaneous tissue placement, a small incision is made in the skin between the scapulae. Using a pair of scissors, make a small incision in the skin, lift the subcutaneous connective tissue. The pump is inserted into the pocket and the skin is closed with a wound clip or suture. Be sure to remove the pump upon completion of the delivery duration or by 10 ± 1 at any time after implantation. This estimate is calculated based on nominal duration. Refer to the equation in Section VI to calculate the exact delivery duration and maximum expiration date for this lot of micro-osmotic pumps.)

For additional information, contact ALZET Technical Support at 600-692-2990 (U.S. and Canada). A video demonstrating several surgical implantation procedure is available at no charge.

VI. Operation of the ALZET Micro-Osmotic Pump

ALZET pumps are precision drug administration tools. This section details the actual pumping rate and fill volume specifications for the lot of Model 1007D pumps being offered. The accuracy of the delivery rate is dependent on the following factors:

1. Temperature
2. Flow moderator
3. Other saline
4. In vitro pumping rates among different pump lots

From DURECT's experience, the coefficient of variation of each pump's output from each pump is analyzed against a standard. Over the 4 to 7 days, each pump is submersed in 0.9% saline at 37°C (± 0.5°C). These pumps are transferred to test tubes containing fresh saline at 37°C (± 0.5°C). Repeat Step 5 for 7 days. This cycle of 7 days pump filling and 7 days pump testing is continued for the duration of delivery. The variation in the rate of pumping is minimal (± 5%). The variation in the rate of pumping is minimal (± 5%)

A. In Vivo Qualification Test

A random sample of 20 ALZET pumps is selected from the same lot which the product you have received. These pumps are filled with a dye solution according to the method described in Section VI. The volume of each ALZET pump is measured to determine flow rate. A flow rate exceeding the pump's rating 10 ± 1 at any time after implantation. This estimate is calculated based on nominal duration. Refer to the equation in Section VI to calculate the exact delivery duration and maximum expiration date for this lot of micro-osmotic pumps.)

Step 1. Analyze the concentration of indicator in each test tube at the start of the experiment. Step 2. Fill the ALZET pump with the indicator solution according to Section VI. Step 3. Place the ALZET pump into a 10 ml test tube filled with 7 ml of isotonic saline and pre-encultased at 37°C (± 0.5°C). Cap the tube to prevent evaporation. Step 4. Record the start time of the incubation. Step 5. Transfer the ALZET pump to a new test tube filled with 15 ml of isotonic saline. Stop the ALZET pump and record the delivery start time. Step 6. Stop the ALZET pump and record the delivery start time. Step 7. Repeat Step 5 for 7 days. Step 8. Repeat Step 5 for 7 days. Step 9. Load each test tube with fresh saline at the start of the next day. Repeat step 5 for 7 days. Step 10. Load each test tube with fresh saline at the start of the next day. Repeat step 5 for 7 days. The procedure is repeated at the end of the delivery time. A. In Vivo Qualification Test

B. Determination of the Pumping Rate

DURECT strongly recommends that ALZET micro-osmotic pumps be slightly larger than that required to assure pumping for the complete 7 days. As a result, a 10 ml of the end of the pumping duration some of the drug solution will remain in the pump. This solution can be aspirated from the pump using a syringe and injected into a 1.0 ml syringe. Recovery of the drug solution can be ensured by flushing the syringe before aspiration with a 1.0 ml syringe. The active agent in the solution which was removed from the reservoir can then be assayed by an appropriate technique. To calculate the average pumping rate, the difference between the initial and residual amount in the pump is divided by the elapsed time.

D. Predicting Pump Performance Outside Mammalian

Ranges of Temperature and Osmolarity

The following equation can be used to predict the pumping rate of ALZET pumps in non-mammalian animals or in those body fluids that are not isotonic with mammals:

\[ Q = \left( \frac{0.156}{T - 18.3} \right) \times P \]  

Where:

- \( Q \) is the pumping rate in ml/hr
- \( T \) is the ambient temperature (°C)
- \( P \) is the osmolality of the solution

The formula is useful in the range of \( T = 25 \) to 47°C and \( P \) = 200 mOsm/kg. At higher osmolarity or mammalian salinity of 300 milliosmolar, the osmotic pressure (\( P \)) is 7.5 at 7.5°C. The equation is predictive within ± 10% of environmental temperature and salinity change that would cause fluctuating delivery rates and are not recommended. This equation is applicable only to the Model 1007D. Note that as \( Q \) decreases in proportion to the environment change, the pumping rate increases.

VII. Use of the ALZET Micro-Osmotic Pump With a Catheter or Brain Kit

The ALZET pump must be able to deliver substances into the venous or arterial circulation, into the brain, or into any organ, tissue, or solid tissue. Attachment to a catheter does not alter the pumping rate of the pump. The ALZET pump can be attached to a catheter tubing as follows:

1. Using a pair of scissors or pliers, break the white flange from the flow moderator in the pump. If using a flow moderator, be careful not to bend or crush the stainless steel tube.

2. Attach the stainless steel tube to a piece of polyethylene or vinyl catheter tubing with a syringe (ID = 0.010 - 0.032 inches). Polyethylene tubing, commonly called PE-10 (ID = 0.032 inches), is a good choice for most applications. After attachment, the catheter should cover about 3 - 4 mm of the length of the tube.

3. Fill the catheter and attached stainless steel tube using a syringe. Leave the syringe attached to the distal end of the catheter.

4. Following the instructions above (Section 5), fill the ALZET pump.

5. Insert the flow moderator all the way into the pump until the catheter is flush with the pump face. Leave the syringe attached to the distal end of the catheter can now be removed.

6. Place the pump in sterile 0.9% saline at 37°C for at least 4 to 6 hours. This is to ensure that the pump will allow the pump to begin operating before implantation, and will minimize the chance of an occlusion or clot forming in the tubing. This step is mandatory in all catheter applications. The pump and catheter can now be implanted.

VII. Verifying the Accuracy of ALZET Micro-Osmotic Pumps

To verify that experimental results are derived from continuous administration of the drug solution, DURECT recommends that ALZET pumps be used for at least 5 days. This will allow the pump to begin operating before implantation, and will minimize the chance of an occlusion or clot forming in the tubing. This step is mandatory in all catheter applications. The pump and catheter can now be implanted.

A. Determination of Average Pumping Rate

The average pumping rate of the ALZET micro-osmotic pump is slightly larger than that required to assure pumping for the complete 7 days. As a result, at the end of the pumping duration some of the drug solution will remain in the pump. This solution can be aspirated from the pump using a syringe and injected into a 1.0 ml syringe. Recovery of the drug solution can be ensured by flushing the syringe before aspiration with a 1.0 ml syringe. The active agent in the solution which was removed from the reservoir can then be assayed by an appropriate technique. To calculate the average pumping rate, the difference between the initial and residual amount in the pump is divided by the elapsed time.

B. Determination of the In Vitro Pumping Rate

DURECT strongly recommends that ALZET micro-osmotic pumps be slightly larger than that required to assure pumping for the complete 7 days. As a result, at the end of the pumping duration some of the drug solution will remain in the pump. This solution can be aspirated from the pump using a syringe and injected into a 1.0 ml syringe. Recovery of the drug solution can be ensured by flushing the syringe before aspiration with a 1.0 ml syringe. The active agent in the solution which was removed from the reservoir can then be assayed by an appropriate technique. To calculate the average pumping rate, the difference between the initial and residual amount in the pump is divided by the elapsed time.

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X. Warranty

Effective for 3 months from the date of shipment, DURECT warrants that the ALZET® Osmotic Pump ("Product") is free from defects in materials and workmanship, and agrees to repair or replace such Product, at its option, if it shall determine in its reasonable discretion after examination that the Product is defective in materials or workmanship, and that such defect in materials or workmanship is the direct cause of the failure of the Product. This warranty does not apply to: (i) Products that are returned for repair after the product warranty period has expired; (ii) Products that have been subject to misuse, neglect, tampering, modification, or misapplication; (iii) Products that have been subject to unauthorized repairs; or (iv) Products that have been subject to unauthorized modifications. This warranty is in lieu of all other warranties, express or implied, and DURECT neither assumes nor accepts any liability in connection therewith. All claims for loss or damage shall be the sole and exclusive remedy for any breach of warranty shall be the replacement, at no cost to the customer, of those units of Product identified as defective.

DURECT Corporation

XI. Additional Technical Information About ALZET Osmotic Pumps

A wealth of information on ALZET osmotic pumps and their uses is available from DURECT Technical Support.

DURECT Technical Support

7147510-13

DURECT Corporation

1-800-692-2990 (toll free in the U.S. and Canada) 408-865-1406 (Facsimile)

techsupport@durect.com (e-mail)

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