This guidance was written prior to the February 27, 1997 implementation of FDA's Good Guidance Practices, GGP's. It does not create or confer rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both. This guidance will be updated in the next revision to include the standard elements of GGP's.

GRZAN

Center for Devices and Radiological Health

Office of Device Evaluation

Division of Gastroenterology/Urology and

General Use Devices

Guidance on 510(k) Submissions for Implanted Infusion Ports

October 1990

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General Submission Requirements

A person proposing to begin the introduction of a new implanted drug infusion/blood sampling port into interstate commerce must submit a premarket notification (510[k]) submission to FDA at least 90 days prior to its introduction.

The general requirements for 510(k) submissions are provided under 21 CFR 807, Subpart E. The 510(k) submissions for implanted ports are evaluated by the General Hospital and Personal Use Devices Branch, Division of Gastroenterology/Urology and General Use Devices.

Overview

A score of implanted ports have been found substantially equivalent through the 510(k) process. The great majority of these ports have been indicated for intravascular (intravenous and intraarterial) use. These substantially equivalent determinations have been based upon comparisons of design specifications with other marketed ports and analysis of performance data derived from in vitro and in vivo testing.

Tens of thousands of ports are now implanted yearly. The design features and clinical experience with ports have matured to a point where FDA believes that the clinical performance of a new intravascular port is predictable provided it has the same intended use and technological characteristics as other marketed ports, satisfactory in vitro testing, and adequate instructions for use.

Thus, in general, in vivo (animal or clinical) data are unnecessary to evaluate equivalence in a 510(k) application of a port for intravascular use that meets the above criteria. However, as detailed below, in certain instances FDA may request in vivo data to establish equivalency.

Total adherence to the specifics of this guidance is not mandatory. It does, however, present important elements to address in a 510(k) submission. Alternatives or modifications to any portion of the guidance may be submitted but should be justified.

Specific Data Requirements for Implanted Ports for Intravascular Use

1. Description of Device

   a. Specifications of port and catheter (specifications must also include catheter physical tests, e.g., tensile, burst)

   b. Engineering drawings (or equivalent)

c. Exact identification of materials, not simply 'stainless steel'

2. Labelling/Instructions for Use

a. Description and specifications of the port components

b. Indications/route of administration, e.g., IV, IA, blood sampling, drug administration, bolus, continuous administration, etc.

Note: If any specific drugs are indicated in the labelling for infusion by the port, the drugs must be approved for the indicated route of administration.

c. Contraindications for those with known or suspected infections, allergies, intolerance to implants, etc.

d. Complications

e. Warnings and Precautions

f. Site selection

g. Implantation

Preparation of the patient
Preparation of the port
Implant procedure
Post-operative care

h. Use of the port for bolus infusion (and continuous, if indicated), or blood sampling, noting needle type and size used, use of heparin, and clearing blockages

3 Table of Comparisons

a. Similar Ports vs. Specifications Grid

Provide a grid comparing the subject device to other ports with comparable characteristics for which equivalence is claimed.

Specifications include dimensions, reservoir volume, catheter ID/OD, materials, septum size, catheter, and catheter lock system.

b. Provide a detailed analysis of comparability based upon the grid.

4. Provide a sample, if possible.

5. In Vitro Test Data

NOTE: All in vitro evaluations should consist of replicate tests and a complete statistical analysis of each segment of testing. Pass/fail criteria must be stated for each test and justified in terms of actual use conditions. The manufacturer must submit the protocol for each test, results and data analysis, explanation for any failures, and conclusions. FDA will provide quantitative information on pass/fail criteria in the next major revision of this guidance (late 1991) based upon the literature and comparative data in 510(k)s. In the interim only qualitative criteria are described.

a. Catheter To Port Connection Tests

Purpose: To test the strength of the catheter to port connection.

Pass: Strength of connection meets specifications based upon worst case in vivo conditions.

Test the catheter to port connection under dry and wet conditions. The wet condition simulates both the external and internal fluid environment to which the catheter to port connection will be exposed, e.g., interstitial fluid, blood, drugs, or flushing solutions. A series of external wet conditions may be tested first followed by exposure of the port to catheter connection to a series of combined external and internal wet conditions. Internal simulation media should include saline, water, dextrose, a heparin-lock, heparinized blood and/or a fluid that approximates the viscosity of blood (see example below of a blood simulation fluid). The external media may include those noted above but must include at least the ~~actual~~ or ~~simulated~~ blood media.

Ports and catheters that are not preattached by the manufacturer must be connected in the wet medium unless labelling indicates connection prior to implantation.

Load conditions vary under actual use. To simulate the variables encountered several types of replicated simulations should be considered. These include:

(1.) axial and lateral loads for each test

(2.) a test where a load equal to the specification is applied for 5-10 seconds

(3.) a test where a load equal to the specification is applied after the connection is exposed for 72 hours to

the wet medium

(4.) an increasing load to failure test

(5.) a test with a minimal load applied for 1-2 weeks with the port in the wet medium to evaluate any creep

(6.) a test with a cyclic load of 1-2 weeks duration

The tests should demonstrate that the catheter meets the specifications or pass/failure criteria for the connection and does not exhibit leaks to air under pressure after loading.

The catheter/port may be removed from the wet medium for connection strength determinations, if necessary, but the connection must remain wet.

Preparation of saline/glycerine solution: distilled, deionized water mixed with 45% glycerine by weight. Titrate with NaCl (2.9 gm/l) for a resistance of approximately 150 ohms at 37°C.

b. Septum Puncture

Purpose: To test the durability of the septum.

Pass: Septum withstands maximum possible punctures (punctures/day x days) plus a safety factor.

Use only the needles listed in labelling on series of ports. Typically, noncoring needles are used. The number of punctures that must be sustained depends upon the life of the port, anticipated punctures per day, plus a safety factor of 1/3. Conduct air leak test after punctures with applied internal pressure equivalent to that encountered in vivo, in a 37°C water bath checking for bubbles. Increase pressure and report the pressure at which the septum exhibits air leaks. Justify the puncture specification based on the data.

c. Port Leak Testing

Purpose: To test the integrity of the whole port.

Pass: Port does not leak under extremes of expected in vivo conditions.

The test regimen should consist of both intermittent and continuous applied pressure to a series of ports to simulate bolus injection and continuous fluid administration by pump. The pressures applied must be

justified in view of those encountered with syringe or pump use and backpressure conditions. Test in 37° C water bath. Check for port seam and septum leaks.

Increase pressure to failure point of port and report maximum pressure attained.

d. Fluid Dynamics Tests

(1.) Clearance Test (see attached)

Purpose: To test clearance kinetics of the port and catheter, and flushing volume requirements of the port and catheter.

Pass: Port clears with reasonable amount of flushing volume and applied syringe pressure.

Attach the catheter to the port, if it is a two piece port. Fill the port with 150 ohm glycerine/saline solution noted above. Put impedance transducer on catheter. Insert non-coring needle in septum. Attach a specified syringe, e.g, 10 ml, with specific volume of flushing solution that has an impedance less than the glycerine/saline solution (e.g. 0.9% NaCl/distilled water giving 50 ohms at 37°C). Submerge the port in a 37°C bath and let the system equilibrate. Instill flushing solution at a specific rate. Record impedance change over time.

The data should be used to gauge the clearance capabilities of the port and adequacy of labelling directions pertaining to flushing.

Results from alternative test methods that address clearance kinetics and flushing requirements may be submitted along with the test protocol.

(2.) Blood Flow Dynamics

Blood is a unique liquid which exhibits flow characteristics and other properties that cannot be fully duplicated by substitute liquids more amenable to laboratory procedures. While the clearance test [5.d.(1.) above] approximates the clearance of a liquid with the viscosity of blood, the test is not an ideal substitute for evaluating actual blood sampling and flushing. FDA encourages manufacturers to develop <u>in vitro</u> methodology to simulate flow patency under repeated blood sampling/flushing and other forward injection/aspiration procedures.

Situations Which Require Additional Data

1. New designs

   Port designs which are not similar to those currently on the market may require additional in vitro and in vivo data. The requirement for additional data will be made on a case by case basis. Such design characteristics could include, for example, a new profile or angle of septum access, a unique catheter lock, or a new type of catheter.

2. New material

   There are several commonly used materials for port construction. A material not previously used for implantable ports will require more extensive biocompatibility, material specifications, and drug interaction data.

3. New route of administration

   a. Until there is further experience with intraperitoneal (IP) use, an IP indication must be supported by clinical data.

   b. Intraspinal administration (epidural or intrathecal catheter implantation) is Class III and requires premarket approval through a PMA application.

4. Comparative or expanded labelling claims, e.g., reduction of infection or occlusion, may require supportive clinical or other data.

5. Indications for pediatric use must be accompanied by a risk analysis for this population and may require supporting data.

ANY COMMENTS ON THIS GUIDANCE DOCUMENT SHOULD BE DIRECTED TO:

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EVALUATION OF CLEARANCE KINETICS OF A PORTAL VASCULAR ACCESS SYSTEM

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ABSTRACT

A portal vascular access system is a totally implantable system comprised of a fluid reservoir with an attached catheter. The system provides easy access for patients requiring a continuous supply of medication or repeated blood sampling. To ensure no obstruction of flow, the system must be flushed to clear the port and catheter, making it important to establish the clearance parameters. This paper describes a method to obtain these parameters using a tetrapolar impedance cell to monitor the relative impedance change using two solutions of different resistivities to fill and flush the system. The resulting impedance dilution curve allows calculation of time delay, dilution time, clearance time and clearance volume. This method and resulting data may be used to characterize a portal vascular access system and provide a basis for comparative analysis of newly introduced systems.

INDEX WORDS: portal vascular access system, clearance volume, impedance dilution curve, clearance parameters

For the patient requiring repeated injections, continuous infusion of drugs or fluids, or repeated blood samples, the portal vascular access system simplifies blood access. The system includes a fluid reservoir commonly called a "port" and a catheter extending from the reservoir (see Figure 1). For venous access, catheters most commonly extend to the superior vena cava through the subclavian vein for venous access. Ports are also used for infusion into the arterial blood vessels, the peritoneum and the central nervous system. Thousands of portal access systems are implanted yearly and the number is increasing. (Figure 1)

Once implanted, a port is accessed by insertion of a needle through the skin into the rubber septum covering the port. Drugs or fluid can be injected or blood can be sampled through the needle. After access is accomplished, but before removing the needle, sterile flushing solution must be injected to clear the port and catheter of drugs or blood. Insufficient flushing may result in clogging or clotting of the catheter and patency will be lost. The volume and flow rate of fluid required for adequate flushing (clearance) depend upon the fluid dynamics of the particular system. The clearance volume is different for different flow rates.

To determine the clearance volume, impedance dilution with two sample solutions of different impedances (one for filling and one for flushing) may be used. After filling the portal access system with the filling solution, injection of a flushing solution of different impedance will produce a record of impedance dilution. Measuring the elapsed time required for a maximum impedance change (reaching

the impedance of the flushing solution) allows calculation of the clearance volume for a given flow rate. This report describes an approach for the measurement of clearance volume of the port reservoir and attached catheter.

METHODS

To detect relative impedance change and thereby calculate the clearance volume of the portal access system, two solutions of different resistivities were prepared: one for filling the system and another for flushing the system. The filling solution chosen was a saline/glycerine mixture, approximating the viscosity of blood, comprised of distilled water mixed with 45% glycerine by weight with added NaCl (2.9 gm/l). The flushing solution chosen was a 0.9% saline mixture. To maintain temperature equilibrium, one beaker containing 0.9% saline and one beaker containing the glycerine/saline solution were placed in a 37°C bath of distilled water.

In order to detect the relative change in impedance which occurs as the flushing solution replaces the filling solution, a tetrapolar impedance cell was implemented at the end of the catheter (see Figure 2). The impedance cell employed four electrodes; current was supplied between the outer two electrodes while the inner two electrodes measured the voltage produced by the current passing through the solution; impedance is the implied voltage divided by the applied current according to Ohm's law. (Figure 2)

The measured resistance, R, is equal to the resistivity of the solution, ρ, multiplied by the cell constant, k. Resistivity of a saline solution can be related to concentration by the equation

$$\rho = 379.1 / C^{0.9149},$$

where C is the concentration of saline at 37°C, and therefore the measured resistance is related to concentration by

$$R = 379.1\ k / C^{0.9149}$$

(Geddes and Baker, 1989). For application in this study, the precise values of ρ and R are not needed since clearance parameters may be obtained from relative impedance change.

A slit of approximately 3 mm in length was cut in the catheter wall near the distal end of each of the two sizes of catheters (1.0 and 1.5 mm ID) which were supplied with the vascular access system studied (VITAL-PORT™ Vascular Access System, Cook Pacemaker Corporation, Leechburg, PA). A tetrapolar impedance cell was affixed in the slit without impeding flow using Locktite 406 (Loctite Corp., Newington, CT) with the electrodes perpendicular to the direction of flow through the catheter. The electrodes were located 63.9 and 67.5 cm distal to the port for the 1.0 and 1.5 mm ID catheters, respectively. The output of the impedance cell was plotted on a strip chart recorder.

Using a resistivity bridge, the measured resistance of the glycerine/saline solution was 160 ohms and the measured resistance of the 0.9% saline solution was 52 ohms. The entire system, including the catheter, was submerged in a 37°C bath. The portal access system was filled with the glycerine/saline solution and allowed to thermally equilibrate. With the chart recorder activated at a paper speed of 25 cm/min and a stable voltage signal from the impedance cell reflecting the impedance of the system filled with the glycerine/saline solution, a constant flow rate (5, 25 or

50 ml/min) of flushing solution (0.9% saline) was delivered by an automatic pump with a 20 cc syringe attached to a 22 gauge 1.5 inch Huber non-coring needle. Measurements were made with the needle placed in various locations in the septum as well as facing various angles with respect to the port outlet tube (needle orientation at 0, 90 and 180 degrees). System filling and flushing were repeated three times for each flow rate (5, 25 and 50 ml/min) for each needle orientation to obtain an average delay time, dilution time, clearance time and clearance volume.

Upon injection of the flushing solution, the relative impedance change between the filling solution and the flushing solution was evident on the strip chart recorder (see Figure 3). Knowing the flow rate of the flushing solution and the paper speed of the strip chart recorder, measurements were made of the delay time, dilution time, total clearance time and total clearance volume. The time delay was measured between the onset of injection of the flushing solution and the onset of an impedance change. This delay is related to the static volume within the reservoir and catheter. Dilution time was measured between the beginning and ending of the impedance change. Total clearance time was measured between the onset of injection and the end of the impedance change. Clearance volume was obtained as the product of flow rate and clearance time, and can be cross checked with the actual injected volume. (Figure 3)

The above procedure was repeated with a 1.5 mm ID catheter attached to the portal access system. Filling and flushing solutions prepared for the 1.5 mm ID catheter had measured resistances of 155 ohms and 52 ohms, respectively. Again, system filling and flushing were repeated three times for each flow rate and needle

orientation to obtain an average delay time, dilution time, clearance time and clearance volume with respect to each flow rate.

In order to relate flow rates (ml/min) to infusion pressure (PSI) in the portal vascular access system, a stainless steel diaphragm pressure transducer (Foxboro/ICT model 1221-08G-K5L) was used to obtain pressures at the needle hub.

RESULTS

For the VITAL-PORT™ Vascular Access System, there were no significant differences in the clearance volume data related to the orientation (angle of the needle with respect to the port outlet tube) using either the attached 1.0 mm or 1.5 mm ID catheters. Although data recorded with respect to the location of the needle in the septum (proximal edge, middle or distal edge) were not exhaustive, no significant differences were noted. Data for each flow rate, independent of needle position, were therefore averaged for each catheter size.

The delay times, dilution times, total clearance times and clearance volumes are tabled for the 1.0 mm ID (see Table I) and the 1.5 mm ID (see Table II) catheters. (Table I) (Table II) In general, higher flow rates require higher clearance volumes, but shorter clearance times and delay times between initial injection and onset of dilution. The 1.5 mm ID catheter requires more clearance volume and clearance time than the 1.0 mm ID catheter.

Infusion pressures for the 1.0 and 1.5 mm ID catheters resulting from flow rates of 50, 25, and 5 ml/min are tabled for the filling (see Table III) and flushing (see Table IV) solutions. As expected, higher flow rates yield higher pressures. The difference in pressures between solutions demonstrates the effect of different viscosities of the filling and flushing solutions. (Table III) (Table IV)

DISCUSSION

Data from this study may be used to determine clearance volumes for the Vital-Port™ Vascular Access System. The procedure, however, may be applicable for any portal vascular access system.

In assessing the data from this study for constant flow rates of 5, 25 and 50 ml/min, it should be noted that a flow rate of 5 ml/min corresponds to a very slow hand-delivered injection rate. A flow rate of 50 ml/min more closely approximates probable hand-delivered flow rates through the system.

While this technique yields the clearance volume of a population sample of systems, the recommended clearance volume should be at least 30% higher than the measured clearance volume obtained in the study, allowing for a safety factor to assure adequate clearance of the system in clinical practice. Assuming the rate of injection by hand approximates 50 ml/min, at least 5.2 ml should be injected to assure clearance (30% increase over the mean value, 3.99 ml found in Table I) for the VITAL-PORT™ Vascular Access System using the 1.0 mm ID (64.0 cm long) catheter. For complete clearance through this same portal system using the 1.5 mm

ID (67.5 cm long) catheter, at least 7.5 ml of solution should be injected (30% increase over the mean value, 5.79 ml at a flow rate of 50 ml/min found in Table II).

The measured and suggested clearance volumes are based on the maximum length catheter. In clinical application, the site for the portal access system is selected and the catheter is cut to the appropriate length, usually 30 cm or less. This results in a reduction in the volume capacity of the system of approximately 0.7 ml using the 1.5 mm ID catheter and 0.3 ml using the 1.0 mm ID catheter. For most situations, to ensure clearance using this portal access system, it would therefore be adequate to inject 4.9 ml (5.2 ml - 0.3 ml) through the portal system using the 1.0 mm ID catheter and 6.8 ml (7.5 ml - 0.7 ml) using the 1.5 mm ID catheter. However, for the sake of simplicity and safety, the maximum clearance volumes may be the recommendation of choice.

Results of this study describe the clearance characteristics for the VITAL-PORT™ Vascular Access System using maximum length pre-attached catheters for injecting solutions with the viscosity of 0.9% saline. For applications using different catheters of varying lengths and/or alternate solutions, flow characteristics and other properties of the solution as well as of the catheter must be kept in mind in determining flow rates, pressures and clearance volumes. Although this study showed no effect of needle orientation for this system, it would be inappropriate to conclude needle orientation is unimportant in other systems. The effect of needle orientation should be considered in each new design. Given all the assumptions are understood and considered, this procedure appears to offer a simple technique for comparative analysis of vascular access systems.

REFERENCES

Geddes LA, Baker LE. *Principles of Applied Biomedical Instrumentation*. 3rd ed. New York: John Wiley & Sons, 1989.

Table I.

CLEARANCE PARAMETERS FOR THE 1.0mm ID CATHETER

FLOW RATE (ml/min)	AVG. DELAY TIME(sec)	AVG. DILUTION TIME(sec)	AVG. CLEARANCE TIME(sec)	AVG. CLEARANCE VOLUME(ml)
5	6.2±0.7	17.6±1.9	23.9±1.8	1.99±0.15
25	1.6±0.2	6.0±0.6	7.5±0.6	3.14±0.23
50	1.1±0.1	3.7±0.5	4.8±0.5	3.99±0.41

Table II.

CLEARANCE PARAMETERS FOR THE 1.5mm ID CATHETER

FLOW RATE (ml/min)	AVG. DELAY TIME(sec)	AVG. DILUTION TIME(sec)	AVG. CLEARANCE TIME(sec)	AVG. CLEARANCE VOLUME(ml)
5	11.6±1.3	29.1±5.5	40.7±6.0	3.39±0.50
25	2.7±0.1	10.0±1.1	12.8±1.0	5.31±0.43
50	1.7±0.2	5.3±0.2	6.9±0.3	5.79±0.24

Table III.

NEEDLE HUB PRESSURE (PSI) FOR
FILLING SOLUTION (45% GLYCERIN IN SALINE)

FLOW RATE (ml/min)	Catheter Size 1.0mm ID	1.5mm ID
5	3.1	2.1
25	17.0	12.2
50	36.0	33.9

Table IV.

NEEDLE HUB PRESSURE (PSI) FOR
FLUSHING SOLUTION (0.9% SALINE)

FLOW RATE (ml/min)	Catheter Size 1.0mm ID	1.5mm ID
5	1.0	0.6
25	6.3	5.0
50	18.8	16.9

FIGURE LEGENDS

Figure 1. Photograph of the VITAL-PORT™ Vascular Access System. A rubber septum covers the port or fluid reservoir to which a supplied catheter is pre-attached through a port outlet tube. The oblong holes in the wall of the port provide suture sites.

Figure 2. Diagram showing set-up for obtaining impedance dilution curves to obtain clearance parameters for the VITAL-PORT™ Vascular Access System.

Figure 3. Impedance dilution curve obtained from a strip chart recorder. The impedance of the filling solution is indicated by Z_1. As the flushing solution is injected, there is a time delay (t) before the change in impedance (ΔZ) occurs. As flushing continues, an impedance dilution curve results over a period of time (T_D). When the port and catheter have been completely flushed or cleared, the impedance of the flushing solution (Z_2) is evident. The clearance time (T) is the period between injection of flushing solution and end of impedance change.

Figure 1.

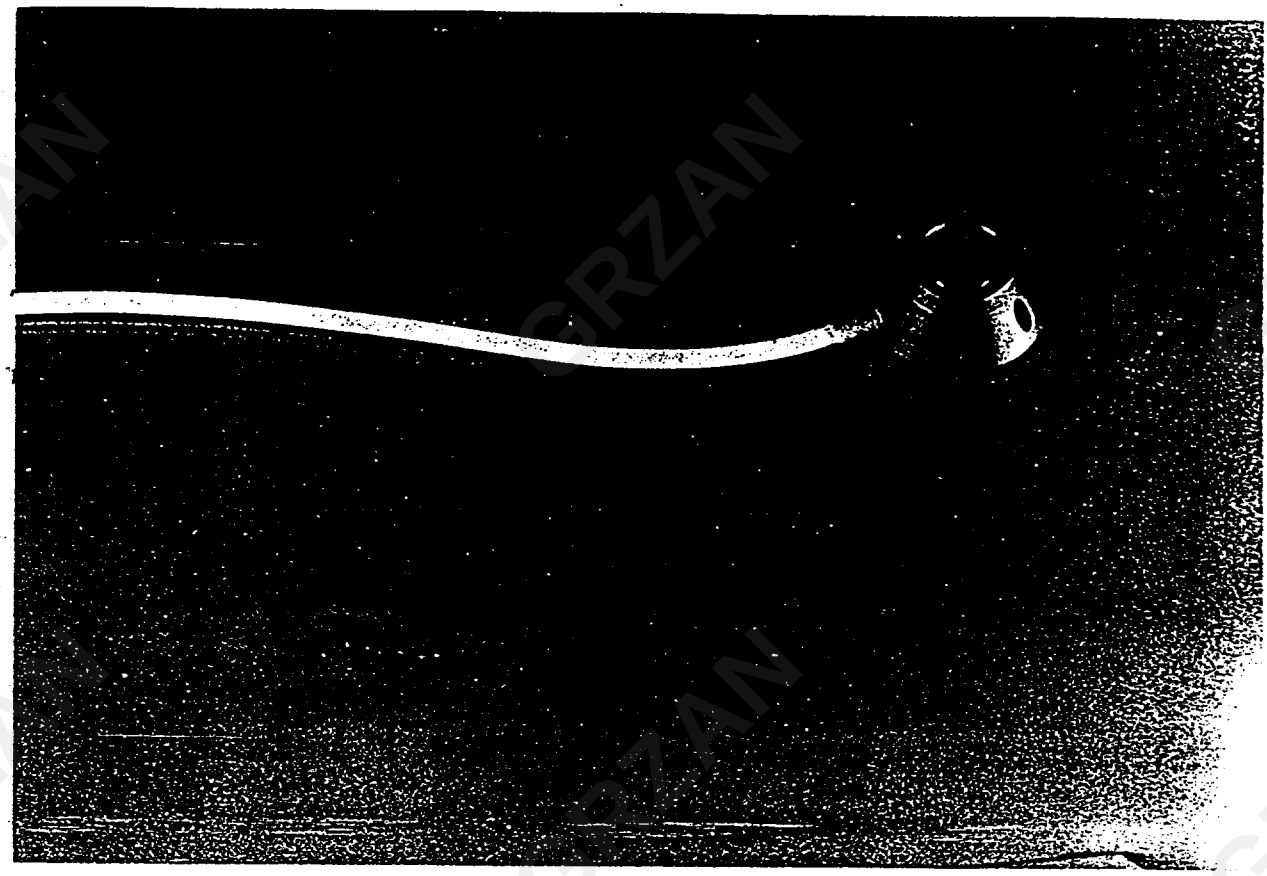


Figure 2.

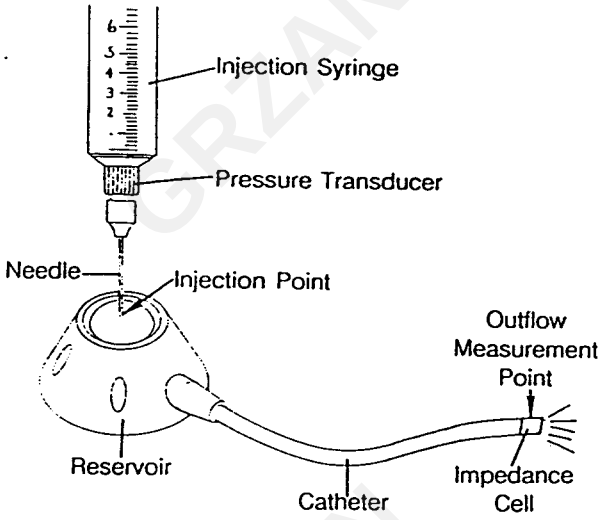
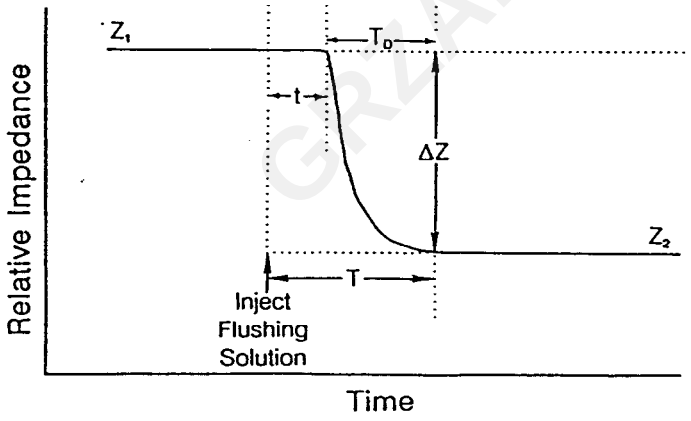

Injection Syringe
Pressure Transducer
Needle
Injection Point
Outflow
Measurement
Point
Reservoir
Catheter
Impedance
Cell

Figure 3.



Where: Z_1 = Impedance of Filling Solution
Z_2 = Impedance of Flushing Solution
t = Time Delay (sec.)
T = Time Required for Clearance (sec.)
T_D = Dilution Time

Figure 1.

