



TheraSphere™ Yttrium-90 Glass Microspheres
Instructions for Use

English

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Instructions for Use

DESCRIPTION

Sterile, single use, Yttrium-90 glass microspheres, 20-30 µm (mean); 22000 to 73000 microspheres per milligram dose dispersed in 0.6 mL pyrogen-free water supplied in 1.0 mL vee-bottom vial enclosed in an acrylic shield; sterile, single-use administration set; reusable administration accessory kit.

PHYSICAL CHARACTERISTICS

The radioactive properties of Yttrium-90 are shown in Table 1.

Table 1
Yttrium-90 Radioactive Properties

Emission	Decay Product	Mean Energy (MeV)	T ½
Pure beta	Zirconium-90	0.9367	64.1 hours

To correct for the physical decay of yttrium-90, the fractions that remain at selected intervals from the time of calibration are shown in Table 2.

Table 2
Yttrium-90 Physical Decay Table
Half-Life 64.1 Hours

Hours	Fraction Remaining	Hours	Fraction Remaining	Hours	Fraction Remaining
-4	1.044	30	0.723	64	0.501
-2	1.022	32	0.707	66	0.490
0*	1.000	34	0.692	68	0.479
2	0.979	36	0.678	70	0.469
4	0.958	38	0.663	72 (Day 3)	0.459
6	0.937	40	0.649	96 (Day 4)	0.354
8	0.917	42	0.635	120 (Day 5)	0.273
10	0.898	44	0.621	144 (Day 6)	0.211
12	0.878	46	0.608	168 (Day 7)	0.163
14	0.860	48 (Day 2)	0.595	192 (Day 8)	0.125
16	0.841	50	0.582	216 (Day 9)	0.097
18	0.823	52	0.570	240 (Day 10)	0.075
20	0.806	54	0.558	264 (Day 11)	0.058
22	0.788	56	0.546	288 (Day 12)	0.044
24 (Day 1)	0.771	58	0.534		
26	0.755	60	0.523		
28	0.739	62	0.511		

*Calibration Time

RADIATION DOSIMETRY

The average range of the radiation in tissue is 2.5 mm. One GBq (27 mCi) of yttrium-90 per kg of tissue gives an initial radiation dose of 13 Gy (1297 rad) per day. The mean life of yttrium-90 is 3.85 days: thus, the radiation dose delivered by yttrium-90 over complete radioactive decay starting at an activity level of 1 GBq (27 mCi) per kg is 50 Gy (5000 rad).

HOW SUPPLIED

TheraSphere™ is steam sterilized and supplied in 6 standard dose sizes: 3 GBq (81 mCi), 5 GBq (135 mCi), 7 GBq (189 mCi), 10 GBq (270 mCi), 15 GBq (405 mCi), 20 GBq (540 mCi). Custom dose sizes are also available in 0.5 GBq increments between 3 and 20 GBq.

TheraSphere™ is supplied with the following accessories:

- 1 single use Administration Set, gamma radiation or ethylene oxide sterilized
- 1 re-usable Administration Accessory Kit, non-sterile

INDICATION

TheraSphere™ is used in the treatment of hepatic neoplasia.

CONTRAINDICATIONS

Use of TheraSphere™ is contraindicated in patients:

- whose Tc-99m macroaggregated albumin (MAA) hepatic arterial perfusion scintigraphy shows any deposition to the gastrointestinal tract that may not be corrected by angiographic techniques
- who show shunting of blood to the lungs that could result in delivery of greater than 16.5 mCi of yttrium-90 to the lungs. Radiation pneumonitis has been seen in patients receiving doses to the lungs greater than 30 Gy in a single treatment
- in whom hepatic artery catheterization is contraindicated; such as patients with vascular abnormalities or bleeding diathesis
- who have severe liver dysfunction or pulmonary insufficiency, and
- who are pregnant.

WARNINGS

A retrospective study of 121 patients from 5 clinical trials has shown that the following 5 Pre-treatment High Risk Factors have been associated with at least 48% of all serious adverse events that were possibly related to use of the device and with 11 of the 12 deaths that were possibly related to use of the device:

- **infiltrative tumor type**
- **“Bulk disease” (tumor volume > 70% of the target liver volume, or tumor nodules too numerous to count)**
- **AST or ALT > 5 times ULN**
- **bilirubin > 2 mg/dL**
- **tumor volume > 50% combined with an albumin < 3 g/dL**

The physician should always take the above-noted Pre-treatment High Risk Factors into consideration for each patient when making decisions regarding the use of TheraSphere™ for treatment.

PRECAUTIONS

- Adequate shielding and precautions for handling radioactive material must be maintained.
- As in the use of any radioactive material, care should be taken to ensure minimum radiation exposure to the patient extraneous to the therapeutic objective and to ensure minimum radiation exposure to workers and others in contact with the patient.
- Since adequate studies have not been performed in animals to determine whether this device affects fertility in males or females, has teratogenic potential, or has other adverse effects on the fetus, this product should not be administered to pregnant or nursing women unless it is considered that the benefits to be gained outweigh the potential hazards.

- Ideally the use of this radioactive device in women of childbearing capability should be performed during the first few (approximately 10) days following the onset of menses.
- Dose rate to personnel should be monitored during administration. Any spills or leaks must be cleaned up immediately and the area monitored for contamination at the end of the procedure.
- The TheraSphere™ dose vial is supplied secured within a clear acrylic vial shield to limit radiation exposure to personnel. The dose rate at the vial shield surface is still high enough to require caution including the use of tongs and a lead shielded container when possible. The TheraSphere™ dose vial should always be stored in a shielded location away from personnel. Ensure the packaging for the TheraSphere™ dose vial and Administration Set are intact before use. If any packages are not intact, discard the item and obtain a new one.

COMPLICATIONS

¹TheraSphere™ and other yttrium-90 microspheres are associated with certain adverse reactions [1,2], for example: chronic pain, ulceration and bleeding, edema and irreversible pulmonary fibrosis.

The use of this product leads to irradiation of both tumourous and normal liver tissue; as a result, patients with diseases that compromise functioning of the non-tumourous liver tissue or with very small lesions scattered throughout the liver may be at greater risk of liver function impairment and hence could experience complications.

DOSAGE AND ADMINISTRATION

Preliminary Patient Evaluation

Prior to the administration of TheraSphere™, the patient should undergo hepatic arterial catheterization using balloon catheterization or other appropriate angiographic techniques to prevent extrahepatic shunting [3]. Following the placement of the hepatic catheter, 75 MBq to 150 MBq (2 mCi to 4 mCi) of Tc-99m MAA is administered into the hepatic artery to determine the extent of A-V shunting to the lungs and to confirm the absence of gastric and duodenal flow. When the possibility of extrahepatic shunting has been evaluated and the patient deemed acceptable for treatment, TheraSphere™ may be administered.

CALCULATION OF DOSE

The recommended dose to the liver is between 80 Gy to 150 Gy (8000 rad to 15000 rad). The amount of radioactivity required to deliver the desired dose to the liver may be calculated using the following formula:

$$\text{Activity Required (GBq)} = \frac{[\text{Desired Dose (Gy)}] [\text{Liver Mass (kg)}]}{50}$$

The liver volume and corresponding liver mass may be determined using CT or ultrasound scans.

Delivery of the desired activity is accomplished by first calculating the activity to be injected using the equation above and then using the Yttrium-90 Physical Decay Table (Table 2) to determine the appropriate time of injection.

For the purpose of ordering TheraSphere™, use the Yttrium-90 Physical Decay Table (Table 2) to determine the appropriate time of injection. For determining the actual liver dose (Gy) delivered to the liver after injection, the following formula is used:

$$\text{Dose (Gy)} = \frac{50 [\text{Injected Activity (GBq)}] [1-F]}{\text{Liver Mass (kg)}}$$

where F is the fraction of injected radioactivity localizing in the lungs, as measured by Tc-99m MAA scintigraphy.

The upper limit of injected activity shunted to the lungs is $F \times A = 0.61$ GBq.

¹Based on clinical and preclinical animal experience

Administration will be accomplished within the product's shelf life. At some point during this period, one of the six dose sizes will allow a patient with liver mass between 0.9 kg and 7.0 kg to be administered sufficient yttrium-90 activity to deliver up to 150 Gy (15000 rad).

When the TheraSphere™ dose vial is received, the site will confirm it is the correct activity for the patient treatment by measuring in a dose calibrator (activimeter).

PATIENT CATHETERIZATION

The following general guidelines are provided to facilitate the selection of the appropriate catheter for the administration of TheraSphere™:

- A catheter with an internal diameter of ≥ 0.5 mm (0.020 inch) is required to deliver TheraSphere™ to the liver. Excessive resistance to flow in the administration system due to a smaller catheter diameter may cause microspheres to be retained in the TheraSphere™ Administration Set and in the catheter. This could result in a misadministration.
- Since the delivery of TheraSphere™ is dependent on blood flow through the hepatic vasculature distal to the catheter tip, it is important that the catheter does not occlude the vessel in which it is placed to effect delivery of TheraSphere™.

TheraSphere™ ADMINISTRATION SET AND TheraSphere™ ADMINISTRATION ACCESSORY KIT

The TheraSphere™ Administration Set (Diagram 1 & 2) consists of a sterile disposable tubing set and one empty sterile vial. The tubing set is made of pre-assembled, sterile components and is for single use only. The pre-assembled tubing set contains a needle plunger assembly and an integrated 20 cc syringe.

The one way valves incorporated in the Administration Set control the flow of liquid such that it will only flow in the appropriate direction. Pulling back on the syringe plunger will fill the syringe from the fluid source. Pushing the syringe plunger will move fluid toward the needle plunger assembly. Prior to the infusion, the Administration Set is manually pre-primed by pushing the sterile flushing solution through the set to purge air from the lines.

The TheraSphere™ Administration Accessory Kit (Diagram 2) contains re-usable accessories including an acrylic box base, top shield, removable side shield and bag hook. The TheraSphere™ Administration Accessory Kit ensures optimal layout of the TheraSphere™ Administration Set and TheraSphere™ dose vial to facilitate monitoring of the infusion process and provides beta radiation shielding.

The Accessory Kit should be placed on a sturdy cart or table that is positioned beside the patient, close to the infusion catheter inlet luer fitting. The extension arm on the Accessory Kit facilitates alignment and positioning of the Administration Set / patient catheter connection.

Throughout the administration procedure, the TheraSphere™ dose vial remains sealed within the clear acrylic vial shield in which it is supplied. The removable plug at the top of the acrylic vial shield provides access to the septum of the TheraSphere™ dose vial. The needle plunger assembly (Diagram 3) is designed to snap into the top of the acrylic shield, and is not easily removed once snapped into place. This provides stability and alignment for the needles which are inserted through the septum when the tabs are pushed down on the plunger assembly.

A constant syringe pressure should be maintained for the duration of each flush, with a flow rate equal to or greater than 20 cc per minute. One flush is 20 cc as indicated on the barrel of the syringe. Using a flow rate of less than 20 cc per minute (i.e. appropriate to the flow of the native vessel) may decrease the delivery efficiency of the administration system. Flushing should be continued until optimal delivery of TheraSphere™ is achieved. A minimum of three flushes for a total of 60 cc is recommended. Infusion pressure should not exceed 30 psi on any flush. The pressure relief valve in the Administration Set has been included to prevent over pressurization.

An electronic dosimeter (RADOS RAD-60 R or equivalent) is mounted in a holder on the Accessory Kit. Radiation monitoring of the Administration Set must be used to determine when optimal delivery has been achieved. The ratio of the dose rate reading taken on the electronic dosimeter before and after the infusion can provide a basis for estimation of the dose delivered to the patient.

In order to minimize the potential of a high radiation hand dose, use a hemostat, forceps or towels/gauze when handling parts of the Administration Set after infusion.

Percentage of dose delivered to the patient can be calculated based on ion-chamber radiation detector measurements of the dose prior to administration, compared to measurements of the waste after administration. Before administration the acrylic shield containing the dose is measured at a distance of 30 cm from the detector. After administration the 2L Nalgene waste container inside the beta shield is measured at a distance of 30 cm from the detector at four rotational positions and these four measurements are averaged. The percentage of dose delivered to the patient can be calculated using the following equation:

$$\text{Percentage of Dose Delivered (\%)} = \left[1 - \frac{\text{Waste Measurement after Administration}}{\text{Dose Vial Measurement before Administration}} \right] \times 100$$

where the *Dose Vial Measurement* is adjusted for the radioactive decay of Y-90 until the time that the *Waste Measurement* is made.

Instructions for TheraSphere™ Infusion

The entire contents of the TheraSphere™ dose vial are administered to the patient.

The administration instructions must be followed to optimize delivery of the calculated dose.

1. Items Required for TheraSphere™ Administration

- Patient prescription for TheraSphere™ (signed Written Directive)
- Ionization survey meter
- Geiger-Mueller (GM) contamination meter
- Spill kit
- A floor drape applied under the cart in the angiography suite.
- A sterile drape placed on the cart.
- Place the following sterile items on the draped cart:
 - Hemostat
 - Scissors
 - Sterile adhesive strips
 - Towels
 - Gauze
- Place the following items on the cart:
 - Administration Set (in packaging)
 - Verify the expiry date.
 - TheraSphere™ Administration Accessory Kit (acrylic box)
 - Remove the top shield
 - Fully extend the stainless steel arm
 - Install the bag hook
 - Electronic dosimeter (RADOS RAD-60 R or equivalent)
 - Turn the dosimeter on and set to mR/h
 - Clip the dosimeter to its bracket on the acrylic box
 - Saline bag (in packaging) or bottle (minimum 100 mL)
 - Alcohol swabs
 - 2L Nalgene waste container with beta shield
 - TheraSphere™ dose vial, in lead pot

2. Administration Set Priming

- Open the Administration Set packaging and remove the Administration Set and 20 mL empty vial.

- Insert the white non-vented spike into the saline bag (or bottle). Hang the saline bag on the bag hook.
- Insert the white vented spike into the empty 20mL vial.
- Remove the RED RUBBER cap from the needle injector assembly. Place the needle injector assembly on a sterile surface.
- Slowly fill and discharge the syringe to remove air from the Administration Set tubing and syringe. Continue priming vigorously with full pressure until there are no bubbles in the lines and there are continuous streams of saline flowing out of both needle holes in the needle injector assembly.
- Fill the syringe when priming is complete.

3. **Dose Vial Preparation**

- Lift the TheraSphere™ dose vial in its lead pot and tilt the lead pot back and forth to 90 degrees to wet any microspheres on the vial septum. Tap the bottom of the lead pot firmly on a hard surface. Place the lead pot into the pot holder in the acrylic box base.
- Remove the lead pot lid and place it upside down on a non-sterile surface.
- Use a hemostat to remove the purple seal from the top of the dose vial acrylic shield. Discard the seal in the Nalgene waste container.
- Use a sterile adhesive strip to remove the dose vial acrylic shield plug. Discard the plug and sterile adhesive strip in the Nalgene waste container.
- Use an alcohol swab and a hemostat to swab the dose vial septum. Discard the swab in the Nalgene waste container.
- Record the dosimeter initial reading for the dose vial (mR/h).
- Measure and record the initial radiation field for the patient, using an ionization survey meter.

4. **Final Assembly**

- Close the white pinch clamp on the outlet tubing between labels 'D' and 'E'.
- Place the empty 20 mL vial in the holder on the acrylic box and push the pressure relief valve tube into gripper clip 'A'.
- Insert the needle injector assembly into the acrylic dose vial shield. Press on the GREEN cap to lock it in place. You will hear or feel a click or snap.
- Place the inlet tubing through slot 'B' in the acrylic box. Place the outlet tubing through slot 'D' in the acrylic box. Loop the tubing around the side and place the fitting into the holder at 'C'.
- Clamp the priming line at label 'C' with the blue pinch clamp. For sets with no blue pinch clamp, clamp the priming line with hemostats (or equivalent).
- Push the YELLOW tabs on the needle injector assembly all the way down, locking the needles into the dose vial. You will hear or feel a click or snap at the bottom of travel.
- Ensure that the side shield is installed on the acrylic box. Place the top shield on the acrylic box with the sloped shield towards slot 'D'. Ensure that the tubing is not pinched or kinked.
- Move the cart close to the patient. Lower the bed to lowest position.
- Place a sterile towel under the extension arm holder 'E', and under holder 'C'.
- Place a sterile towel across the gap between the acrylic box and the patient.
- The Interventional Radiologist (IR) will flush the infusion catheter to ensure flow. Replace the infusion catheter if it is damaged or does not have satisfactory flow. Do not use a catheter extension or extra fittings. Replace the catheter if it is too short.
- Disconnect the outlet tubing labeled 'E' from the priming tubing at holder 'C'. Firmly connect the outlet tubing 'E' to the catheter.
- Place the catheter connection into the slotted holder 'E' at the end of the extended arm. Outlet tubing 'E' must be above the holder, with the infusion catheter hanging vertically below.
- The IR will verify the infusion catheter position.
- Release the white pinch clamp from the outlet tubing. Dents in tubing may be reduced by rolling outlet tubing with fingers.

5. **TheraSphere™ Administration**

ATTENTION: Beta radiation fields can be very high during microsphere transfer. Stand behind beta shielding or maintain distance.

- Record the starting time of the administration.
- Infuse TheraSphere™ Y-90 glass microspheres using steady pressure on the syringe plunger. Infuse continuously until the syringe is empty (≥ 20 cc per minute).

NOTE: If the infusion pressure is over 30 psi, excess fluid will drip into the vented 20 mL vial. If this oc-

curs, reduce the pressure being applied on the syringe until no flow is seen going into the vented vial. If the syringe flow is <20 cc per minute (i.e. appropriate to the flow of the native vessel) this may decrease the delivery efficiency of the administration system and result in higher residual in waste.

- Observe the outlet line and catheter for proper operation. If a problem is observed, inform the team and take corrective action.
- Re-fill the syringe for subsequent flushes by pulling back on the syringe plunger. A minimum of 3 flushes (60 cc total) are recommended. Continue flushes until the desired dosimeter reading is achieved.
- Record the number of flushes completed.
- Record the time that administration was completed.
- Record the final dosimeter reading.
- Measure and record the final radiation field for the patient using an ionization survey meter.

6. **Disassembly**

- Cut the inlet tubing at the indicated position.
- Remove the acrylic box top shield and side shield.
- The IR will remove the infusion catheter from the patient and lift the catheter connection out of the extended holder 'E'. Do not disconnect the catheter from the outlet tubing. Use care to control the tip of the infusion catheter and guide catheter as these may be contaminated with microspheres. Use gauze, a small towel, or hemostat to handle the catheters for radiation protection. Any item that has come in contact with microspheres is considered contaminated.
- Place all contaminated waste into the Nalgene waste container (in its beta shield), including the following:
 - Infusion catheter and guide catheter with attached tubing and towels/gauze
 - dose vial with attached needle injector assembly
 - lift the lead pot and dump out the dose vial.
 - contaminated items such as gauze, towels and gloves
- Cap the Nalgene waste container and place the acrylic lid on the beta shield. Remove for measurements to determine percent delivery and for disposal.
- Use a GM contamination meter to check IR's hands for contamination.
- Survey all staff leaving the room with the GM contamination meter.

7. **Cleanup and Waste Disposal**

- Use a GM contamination meter to check for contamination on the cart, lead pot, equipment, and the areas under the catheter connection and cart.

NOTE: Radiation from fluoroscopy, the patient, and the waste container will affect the ability to detect and measure contamination.

- Decontaminate and/or dispose of items as appropriate.
- As required, clean the TheraSphere™ acrylic box with water, mild soap and a clean soft cloth. Alcohol wipes may be used (minimize alcohol contact with glued joints – alcohol degrades the glue over an extended time). Chlorine (bleach) disinfectants are also acceptable. Always use a clean soft cloth. **Do not use** industrial cleaner wipes, ammonia or abrasives to clean the acrylic parts.
- Replace the top and side shields on the acrylic box. Retract the extension arm and remove the bag hook. Turn off the dosimeter. Store the kit.

Troubleshooting

Problem	Action
<p>1. Difficulty priming the Administration Set.</p>	<p>Verify that the tubing in the Administration Set is not pinched or kinked. Verify that the pinch clamp is not closed.</p> <p>The first priming flush should be performed very slowly to prevent small bubbles from forming in tubing and fittings. Subsequent priming flushes should be vigorous with full pressure.</p> <p>If saline leakage is observed, ensure connections are tight.</p> <p>If the issue cannot be identified and corrected, replace the Administration Set with a new one. Notify the manufacturer of the problem.</p>
<p>2. Leakage that may contain microspheres</p>	<p>Attention: Any leakage from the dose vial, injector assembly, tubing 'D' through 'E', or the catheter connection at 'E' is likely to contain microspheres.</p> <p>Assess the extent of the leak. Ensure that the needle injector is properly inserted into the dose vial. If warranted, abort the infusion, disassemble the Administration Set and commence decontamination procedures. During decontamination, investigate the cause of the leak.</p>
<p>3. Leakage of saline during infusion</p>	<p>Leakage observed from the syringe, the saline bag/bottle, or tubing lines 'A', 'B' and 'C' will only contain saline. If saline leakage is observed during TheraSphere™ Administration, maintain steady pressure on the syringe.</p> <p>Do not stop the flush. At the end of the flush, address the saline leakage. Ensure that priming tube 'C' is clamped. Ensure connection to the syringe is tight. Adjust the saline bag or bottle connection.</p>
<p>4. Blood begins to flow back to the TheraSphere™ dose vial, when the catheter is connected and the syringe is not being pushed.</p>	<p>This indicates that one of the fittings or the TheraSphere™ dose vial septum is compromised. The procedure should be aborted if the issue cannot be identified and corrected. If issue has been identified and corrected, continue with administrations and observe the system for possible leaks (see Problem 2).</p>
<p>5. Excessive fluid flow resistance is experienced during infusion</p> <p>or</p> <p>Difficulty achieving the desired dosimeter reading.</p>	<p>Verify that the white pinch clamp is open. Verify that the tubing between the syringe and dose vial are not pinched or kinked. Verify that the tubing between the dose vial and catheter are not pinched or kinked. Verify that the yellow tabs are pushed all the way down.</p> <p>Apply sufficient pressure on the syringe to cause fluid to flow into the pressure relief vial.</p> <p>Apply and release pressure on the syringe several times rapidly. This may clear a collection of microspheres at the tip of the outlet needle.</p> <p><u>Close the white pinch clamp</u> before performing any actions with the catheter. Verify that there is no blood coagulation or damage in the catheter.</p> <p>Attention: There may be microspheres in the outlet line and catheter. Use standard radiation safety methods to assess the components before handling. Use remote handling tools as appropriate.</p>

HANDLING AND STORAGE

Each TheraSphere™ dose vial contains one of six available dose sizes of yttrium-90, a high-energy beta emitter. Even with low-density materials such as the acrylic vial shield, the attenuation of beta particles gives rise to Bremsstrahlung radiation that requires lead shielding.

Users should avoid exposure by leaving the vial in the acrylic vial shield, and by leaving the acrylic vial shield in the lead pot as much as possible. The use of additional shielding is recommended. Finger-ring dosimeters should be worn in the orientation most likely to record the highest exposure to the fingers.

The TheraSphere™ dose vial should not be removed from its acrylic vial shield. It should be stored upright in the acrylic vial shield and lead pot in which it is packaged. The TheraSphere™ dose vial, TheraSphere™ Administration Set, and TheraSphere™ Administration Accessory Kit should be stored at room temperature. The requirements of the applicable regulatory agency for safe handling and storage of radioactive materials should be consulted and must be followed.

DISTRIBUTION

TheraSphere™ is manufactured and distributed for Biocompatibles:



Biocompatibles UK Ltd, a BTG International group company
Chapman House
Farnham Business Park
Weydon Lane, Farnham
Surrey GU9 8QL UK
www.therasphere.com



Year of authorization to affix the CE mark: 2005

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Explanation of Symbols on TheraSphere™ Product Labels



Product fulfils Conformity Assessment according to Council Directive 90/385/EEC, verified by BSi.

Act: Activity. The radioactive dose size provided on the lead pot and acrylic product shield labels.

Cal: Calibration date. This is provided on the lead pot and acrylic product shield labels.

Mass: Mass. The mass of the microspheres is on the lead pot and acrylic product shield labels.

QTY 1

Package contains 1 item.

Symbol Relevant to TheraSphere™ Product

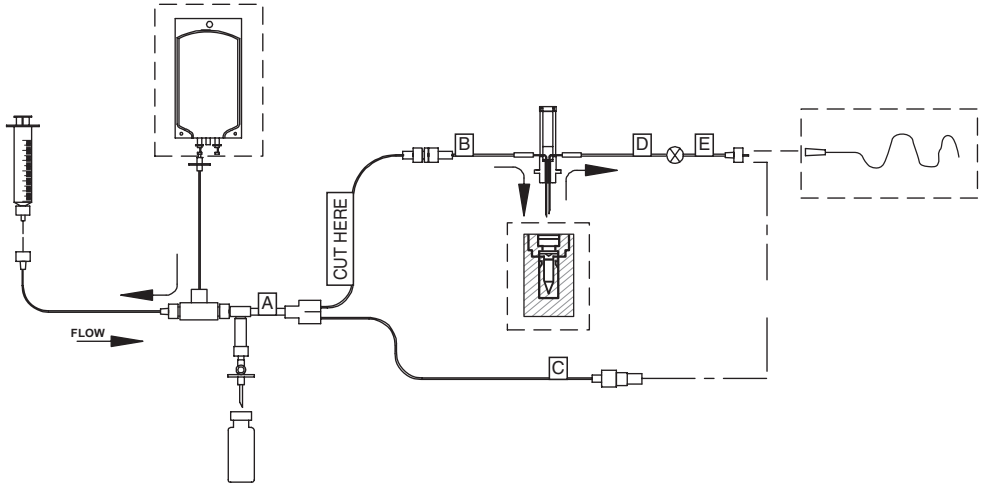


Does not contain latex.

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Diagram 1
TheraSphere™ Administration Set Configuration



Items in dashed boxes are not supplied with the Administration Set

Diagram 2
TheraSphere™ Administration Accessory Kit
(shown assembled with TheraSphere™ Administration Set)

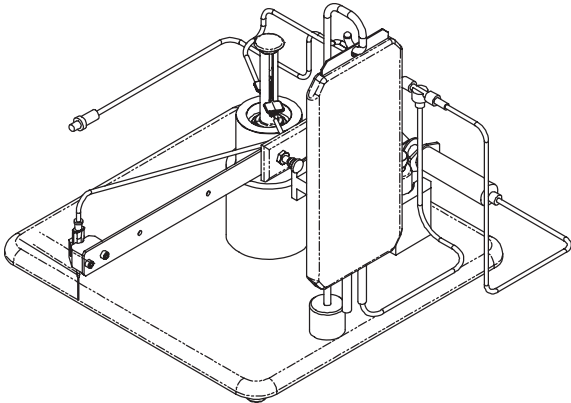
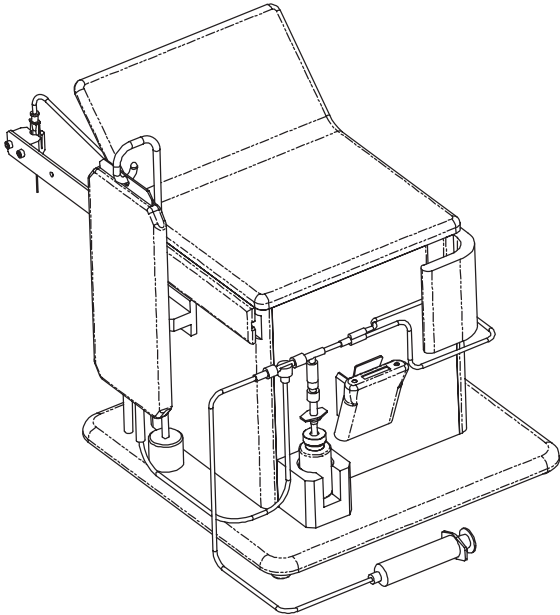


Diagram 3
Illustration of the Plunger Assembly Inserted into the Dose Vial in the Acrylic Shield

