BioPearl™ Microspheres Loading Instructions

In order to minimize the risk of microbial contamination, loading and preparation of BioPearl Microspheres must be carried out using strict aseptic technique under controlled conditions.

Throughout the loading process, avoid introduction of air bubbles into the system and eliminate any that occur.

	Doxorubicin Powder for Injection	**Doxorubicin Liquid for Injection**	**Epirubicin for Injection**	**Idarubicin Liquid for Injection**
Step 1: **DRUG PREPARATION**	Use a maximum of **75mg** of Doxorubicin Powder for Injection as received from the manufacturer. Reconstitute every 25mg of Doxorubicin Powder with 1ml of sterile water for injection (25mg/ml). Mix well, until **ALL** solid particles are dissolved.	Use a maximum of **75mg** of Doxorubicin Liquid for Injection as received from the manufacturer. (i.e. 37.5ml of 2mg/ml concentration)	Use a maximum of **50mg** of Epirubicin for Injection as received from the manufacturer. (i.e. 25 ml of 2mg/ml concentration)	Use a maximum of **10mg** of Idarubicin Liquid for Injection as received from the manufacturer. (i.e. 10ml of 1mg/ml concentration)
Step 2: **MICROSPHERE RECONSTITUTION**	➢ Fill a user-supplied 20ml syringe with 5-10ml of physiological buffered saline or saline. ➢ Connect the syringe to a needle of 20-gauge diameter or larger. ➢ Carefully insert the needle of the syringe through the stopper of the vial. Take care not to core the rubber stopper. ➢ Inject the fluid from the syringe. Proper aspiration and/or venting techniques, as approved by the healthcare facility, may be used for easier injection of reconstitution medium into the vial. Prior to injecting the reconstitution fluid, it may be necessary to manually aspirate air from the vial into the syringe. ➢ Remove the needle and syringe. Shake the vial so that the liquid contacts the stopper at least 10 times. ➢ Wait a minimum of 10 minutes and no longer than 15 minutes to allow the BioPearl Microspheres to reconstitute and expand to their intended size. ➢ Gently shake the vial to make the contents homogenous and use the user-provided syringe and needle to gently aspirate the entire contents of the vial into the syringe. If air was previously aspirated from the vial, gentle injection of air using the syringe prior to aspirating the contents of the vial will ensure an easier aspiration of vial contents into the syringe. Take care not to core the rubber stopper.	➢ Fill a user-supplied 50ml or larger syringe with 5-10ml of physiological buffered saline or saline. ➢ Connect the syringe to a needle of 20-gauge diameter or larger. ➢ Carefully insert the needle of the syringe through the stopper of the vial. Take care not to core the rubber stopper. ➢ Inject the fluid from the syringe. Proper aspiration and/or venting techniques, as approved by the healthcare facility, may be used for easier injection of reconstitution medium into the vial. Prior to injecting the reconstitution fluid, it may be necessary to manually aspirate air from the vial into the syringe. ➢ Remove the needle and syringe. Shake the vial so that the liquid contacts the stopper at least 10 times. ➢ Wait a minimum of 10 minutes and no longer than 15 minutes to allow the BioPearl Microspheres to reconstitute and expand to their intended size. ➢ Gently shake the vial to make the contents homogenous and use the user-provided syringe and needle to gently aspirate the entire contents of the vial into the syringe. If air was previously aspirated from the vial, gentle injection of air using the syringe prior to aspirating the contents of the vial will ensure an easier aspiration of vial contents into the syringe. Take care not to core the rubber stopper.	➢ Fill a user-supplied 50ml or larger syringe with 5-10ml of physiological buffered saline or saline. ➢ Connect the syringe to a needle of 20-gauge diameter or larger. ➢ Carefully insert the needle of the syringe through the stopper of the vial. Take care not to core the rubber stopper. ➢ Inject the fluid from the syringe. Proper aspiration and/or venting techniques, as approved by the healthcare facility, may be used for easier injection of reconstitution medium into the vial. Prior to injecting the reconstitution fluid, it may be necessary to manually aspirate air from the vial into the syringe. ➢ Remove the needle and syringe. Shake the vial so that the liquid contacts the stopper at least 10 times. ➢ Wait a minimum of 10 minutes and no longer than 15 minutes to allow the BioPearl Microspheres to reconstitute and expand to their intended size. ➢ Gently shake the vial to make the contents homogenous and use the user-provided syringe and needle to gently aspirate the entire contents of the vial into the syringe. If air was previously aspirated from the vial, gentle injection of air using the syringe prior to aspirating the contents of the vial will ensure an easier aspiration of vial contents into the syringe. Take care not to core the rubber stopper.	➢ Fill a user-supplied 20ml syringe with 5-10ml of physiological buffered saline or saline. ➢ Connect the syringe to a needle of 20-gauge diameter or larger. ➢ Carefully insert the needle of the syringe through the stopper of the vial. Take care not to core the rubber stopper. ➢ Inject the fluid from the syringe. Proper aspiration and/or venting techniques, as approved by the healthcare facility, may be used for easier injection of reconstitution medium into the vial. Prior to injecting the reconstitution fluid, it may be necessary to manually aspirate air from the vial into the syringe. ➢ Remove the needle and syringe. Shake the vial so that the liquid contacts the stopper at least10 times. ➢ Wait a minimum of 10 minutes and no longer than 15 minutes to allow the BioPearl Microspheres to reconstitute and expand to their intended size. ➢ Gently shake the vial to make the contents homogenous and use the user-provided syringe and needle to gently aspirate the entire contents of the vial into the syringe. If air was previously aspirated from the vial, gentle injection of air using the syringe prior to aspirating the contents of the vial will ensure an easier aspiration of vial contents into the syringe. Take care not to core the rubber stopper.
Step 3: **DRUG LOADING**	➢ Stand the syringe containing BioPearl Microspheres upright so that the reconstituted microspheres settle on the plunger (approximately 5 minutes). ➢ Use a 5 micron filter needle or any other transfer device used in the pharmacy to expel most of the saline, leaving 3ml total contents in the syringe. **NOTE: DO NOT compress the microspheres by leaving 3ml of the content in the syringe (2ml of microspheres and 1ml of saline).** ➢ Within the first 20 minutes after adding fluid to the BioPearl Microspheres (see Step 2), transfer a maximum of 75mg of Doxorubicin into the syringe containing BioPearl Microspheres and shake the syringe until contents are homogenous (approximately 1 minute).	➢ Stand the syringe containing BioPearl Microspheres upright so that the reconstituted microspheres settle on the plunger (approximately 5 minutes). ➢ Use a 5 micron filter needle or any other transfer device used in the pharmacy to expel most of the saline, leaving 3ml total contents in the syringe. **NOTE: DO NOT compress the microspheres by leaving 3ml of the content in the syringe (2ml of microspheres and 1ml of saline).** ➢ Within the first 20 minutes after adding fluid to the BioPearl Microspheres (see Step 2), transfer a maximum of 75mg of Doxorubicin into the syringe containing BioPearl Microspheres and shake the syringe until contents are homogenous (approximately 1 minute).	➢ Stand the syringe containing BioPearl Microspheres upright so that the reconstituted microspheres settle on the plunger (approximately 5 minutes). ➢ Use a 5 micron filter needle or any other transfer device used in the pharmacy to expel most of the saline, leaving 3ml total contents in the syringe. **NOTE: DO NOT compress the microspheres by leaving 3ml of the content in the syringe (2ml of microspheres and 1ml of saline).** ➢ Within the first 20 minutes after adding fluid to the BioPearl Microspheres (see Step 2), transfer a maximum of 50mg of Epirubicin into the syringe containing BioPearl Microspheres and shake the syringe until contents are homogenous (approximately 1 minute).	➢ Stand the syringe containing BioPearl Microspheres upright so that the reconstituted microspheres settle on the plunger (approximately 5 minutes). ➢ Use a 5 micron filter needle or any other transfer device used in the pharmacy to expel most of the saline, leaving 3ml total contents in the syringe. **NOTE: DO NOT compress the microspheres by leaving 3ml of the content in the syringe (2ml of microspheres and 1ml of saline).** ➢ Within the first 20 minutes after adding fluid to the BioPearl Microspheres (see Step 2), transfer a maximum of 10mg of Idarubicin into the syringe containing BioPearl Microspheres and shake the syringe until contents are homogenous (approximately 1 minute).

	➢ Transfer 3ml of the 25mg/ml drug solution for a total of 75mg of Doxorubicin ➢ Allow the microspheres to load for the duration of the loading period at room temperature, agitating the microspheres occasionally. Protect the microspheres from light during the loading period. This can be accomplished by wrapping the syringe in foil. Refer to the table below for recommended loading times **NOTE: When loaded with Doxorubicin per Steps 1-3, BioPearl Microspheres may shrink or swell up to 10% of their original unloaded diameter.**	➢ Transfer 37.5ml of the 2mg/ml drug solution for a total of 75mg of Doxorubicin ➢ Allow the microspheres to load for the duration of the loading period at room temperature, agitating the microspheres occasionally. Protect the microspheres from light during the loading period. This can be accomplished by wrapping the syringe in foil. Refer to the table below for recommended loading times **NOTE: When loaded with Doxorubicin per Steps 1-3, BioPearl Microspheres may shrink or swell up to 10% of their original unloaded diameter.**	➢ Transfer 25ml of the 2mg/ml drug solution for a total of 50mg of Epirubicin ➢ Allow the microspheres to load for the duration of the loading period at room temperature, agitating the microspheres occasionally. Protect the microspheres from light during the loading period. This can be accomplished by wrapping the syringe in foil. Refer to the table below for recommended loading times **NOTE: When loaded with Epirubicin per Steps 1-3, BioPearl Microspheres may shrink or swell up to 10% of their original unloaded diameter.**	➢ Transfer 10ml of the 1mg/ml drug solution for a total of 10mg of Idarubicin ➢ Allow the microspheres to load for the duration of the loading period at room temperature, agitating the microspheres occasionally. Protect the microspheres from light during the loading period. This can be accomplished by wrapping the syringe in foil. Refer to the table below for recommended loading times **NOTE: When loaded with Idarubicin per Steps 1-3, BioPearl Microspheres may shrink or swell up to 15% of their original unloaded diameter.**
	NOTE: At this point, the product may be stored under refrigerated conditions (2-8ºC) and protected from light for up to 24 hours prior to use, starting from the time of reconstitution (Step 2). Do not store the microspheres dry. Leave at least 1ml of drug supernatant in the syringe.			
Step 4: **SPLIT INTO TWO SYRINGES**	➢ After loading (refer to table below for loading times), gently mix and transfer into two 20ml syringes (approximately half the total volume in each 20ml syringe). ➢ Stand both 20ml syringes vertically on the plunger for approximately 5 minutes to allow the microspheres to settle. ➢ After the microspheres settle, verify that the volume of microspheres is approximately equal in both syringes (each syringe should have approximately 1ml of microspheres). ➢ If the volume of microspheres is not equal, gently re-transfer all product to a 20ml syringe and restart Step 4 from the beginning. ➢ Repeat as necessary until both 20ml syringes contain approximately 1ml of microspheres.	➢ After loading (refer to table below for loading times), gently mix and transfer into two 20ml syringes (approximately half the total volume in each 20ml syringe). ➢ Stand both 20ml syringes vertically on the plunger for approximately 5 minutes to allow the microspheres to settle. ➢ After the microspheres settle, verify that the volume of microspheres is approximately equal in both syringes (each syringe should have approximately 1ml of microspheres). ➢ If the volume of microspheres is not equal, gently re-transfer all product to a 50ml syringe and restart Step 4 from the beginning. ➢ Repeat as necessary until both 20ml syringes contain approximately 1ml of microspheres.	➢ After loading (refer to table below for loading times), gently mix and transfer into two 20ml syringes (approximately half the total volume in each 20ml syringe). ➢ Stand both 20ml syringes vertically on the plunger for approximately 5 minutes to allow the microspheres to settle. ➢ After the microspheres settle, verify that the volume of microspheres is approximately equal in both syringes (each syringe should have approximately 1ml of microspheres). ➢ If the volume of microspheres is not equal, gently re-transfer all product to a 50ml syringe and restart Step 4 from the beginning. ➢ Repeat as necessary until both 20ml syringes contain approximately 1ml of microspheres.	➢ After loading (refer to table below for loading times), gently mix and transfer into two 20ml syringes (approximately half the total volume in each 20ml syringe). ➢ Stand both 20ml syringes vertically on the plunger for approximately 5 minutes to allow the microspheres to settle. ➢ After the microspheres settle, verify that the volume of microspheres is approximately equal in both syringes (each syringe should have approximately 1ml of microspheres). ➢ If the volume of microspheres is not equal, gently re-transfer all product to a 20ml syringe and restart Step 4 from the beginning. ➢ Repeat as necessary until both 20ml syringes contain approximately 1ml of microspheres.
Step 5: **EXPEL SUPERNATANT**	➢ Before expelling supernatant, ensure that both 20ml syringes have stood vertically on the plunger for approximately 5 minutes to allow microspheres to settle. ➢ Use a 5 micron filter needle or any other transfer device used in the pharmacy to expel the drug supernatant from the syringe. **NOTE: DO NOT compress the microspheres.**	➢ Before expelling supernatant, ensure that both 20ml syringes have stood vertically on the plunger for approximately 5 minutes to allow microspheres to settle. ➢ Use a 5 micron filter needle or any other transfer device used in the pharmacy to expel the drug supernatant from the syringe. **NOTE: DO NOT compress the microspheres.**	➢ Before expelling supernatant, ensure that both 20ml syringes have stood vertically on the plunger for approximately 5 minutes to allow microspheres to settle. ➢ Use a 5 micron filter needle or any other transfer device used in the pharmacy to expel the drug supernatant from the syringe. **NOTE: DO NOT compress the microspheres.**	➢ Before expelling supernatant, ensure that both 20ml syringes have stood vertically on the plunger for approximately 5 minutes to allow microspheres to settle. ➢ Use a 5 micron filter needle or any other transfer device used in the pharmacy to expel the drug supernatant from the syringe. **NOTE: DO NOT compress the microspheres.**
	NOTE: After the required loading time, the solution in the syringe may retain some coloration. This is NOT an indication that the BioPearl Microspheres have failed to load.			
Step 6: **ADD NON-IONIC CONTRAST & STERILE WATER SOLUTION**	Add a minimum of 20ml of 50:50 non-ionic contrast and sterile water solution to a 50-60ml syringe.	Add a minimum of 20ml of 50:50 non-ionic contrast and sterile water solution to a 50-60ml syringe.	Add a minimum of 20ml of 50:50 non-ionic contrast and sterile water solution to a 50-60ml syringe.	Add a minimum of 20ml of 50:50 non-ionic contrast and sterile water solution to a 50-60ml syringe.
	NOTE: At this point, the BioPearl Microspheres must be used – DO NOT store for later use.			
	NOTE: Only the non-ionic contrasts listed in the contrast table below have been evaluated for suspension and delivery characteristics and are recommended for use. Use of a contrast outside of those listed may lead to unpredictable suspension behavior.			

Step 7: **AGITATE AND SUSPEND PRIOR TO USE**	➢ Connect one of the 20ml syringes (containing approximately 1ml of drug-loaded microspheres) and the 50-60ml syringe (containing a minimum of 20ml of 50:50 non-ionic contrast and sterile water solution) through a 3-way stopcock and agitate contents between the two syringes until homogeneous suspension is achieved. The plungers do not need to be fully depressed during mixing, as this risks dispersing any small air bubbles throughout the microsphere suspension. ➢ After mixing the non-ionic contrast and sterile water solution with the microspheres, **wait 10 minutes** to allow the solution to equilibrate. **NOTE: DO NOT introduce air into the system.**	➢ Connect one of the 20ml syringes (containing approximately 1ml of drug-loaded microspheres) and the 50-60ml syringe (containing a minimum of 20ml of 50:50 non-ionic contrast and sterile water solution) through a 3-way stopcock and agitate contents between the two syringes until homogeneous suspension is achieved. The plungers do not need to be fully depressed during mixing, as this risks dispersing any small air bubbles throughout the microsphere suspension. ➢ After mixing the non-ionic contrast and sterile water solution with the microspheres, **wait 10 minutes** to allow the solution to equilibrate. **NOTE: DO NOT introduce air into the system**	➢ Connect one of the 20ml syringes (containing approximately 1ml of drug-loaded microspheres) and the 50-60ml syringe (containing a minimum of 20ml of 50:50 non-ionic contrast and sterile water solution) through a 3-way stopcock and agitate contents between the two syringes until homogeneous suspension is achieved. The plungers do not need to be fully depressed during mixing, as this risks dispersing any small air bubbles throughout the microsphere suspension. ➢ After mixing the non-ionic contrast and sterile water solution with the microspheres, **wait 10 minutes** to allow the solution to equilibrate. **NOTE: DO NOT introduce air into the system.**	➢ Connect one of the 20ml syringes (containing approximately 1ml of drug-loaded microspheres) and the 50-60ml syringe (containing a minimum of 20ml of 50:50 non-ionic contrast and sterile water solution) through a 3-way stopcock and agitate contents between the two syringes until homogeneous suspension is achieved. The plungers do not need to be fully depressed during mixing, as this risks dispersing any small air bubbles throughout the microsphere suspension. ➢ After mixing the non-ionic contrast and sterile water solution with the microspheres, **wait 10 minutes** to allow the solution to equilibrate. **NOTE: DO NOT introduce air into the system.**
Step 8: **DELIVERY**	➢ It is recommended to use a 1 mL luer-lock syringe for delivery for optimal pressure (sizes greater than 1 mL may increase chance of catheter blockages or increase in delivery pressure) ➢ Re-agitate microsphere suspension between the delivery syringe and suspension syringe a minimum of 5 times before each delivery. ➢ It is highly recommended to use a pulsatile delivery method for delivery. Non-pulsatile delivery may increase the likelihood of microsphere aggregation or catheter occlusion. ➢ It is recommended to flush the delivery catheter intermittently with saline between injections or after pauses in delivery for angiography. ➢ During the treatment procedure, ensure that BioPearl microspheres are still in suspension. Re-agitate suspension syringe as necessary. ➢ During the treatment procedure, the recommended solution delivery rate is 1 mL per minute. ➢ Once delivery is completed for the first syringe, if required by the physician for use, prepare the second 20 mL syringe of BioPearl (containing approximately 1 mL of drug-loaded microspheres) starting at Step 6.	➢ It is recommended to use a 1 mL luer-lock syringe for delivery for optimal pressure (sizes greater than 1 mL may increase chance of catheter blockages or increase in delivery pressure) ➢ Re-agitate microsphere suspension between the delivery syringe and suspension syringe a minimum of 5 times before each delivery. ➢ It is highly recommended to use a pulsatile delivery method for delivery. Non-pulsatile delivery may increase the likelihood of microsphere aggregation or catheter occlusion. ➢ It is recommended to flush the delivery catheter intermittently with saline between injections or after pauses in delivery for angiography. ➢ During the treatment procedure, ensure that BioPearl microspheres are still in suspension. Re-agitate suspension syringe as necessary. ➢ During the treatment procedure, the recommended solution delivery rate is 1 mL per minute. ➢ Once delivery is completed for the first syringe, if required by the physician for use, prepare the second 20 mL syringe of BioPearl (containing approximately 1 mL of drug-loaded microspheres) starting at Step 6.	➢ It is recommended to use a 1 mL luer-lock syringe for delivery for optimal pressure (sizes greater than 1 mL may increase chance of catheter blockages or increase in delivery pressure) ➢ Re-agitate microsphere suspension between the delivery syringe and suspension syringe a minimum of 5 times before each delivery. ➢ It is highly recommended to use a pulsatile delivery method for delivery. Non-pulsatile delivery may increase the likelihood of microsphere aggregation or catheter occlusion. ➢ It is recommended to flush the delivery catheter intermittently with saline between injections or after pauses in delivery for angiography. ➢ During the treatment procedure, ensure that BioPearl microspheres are still in suspension. Re-agitate suspension syringe as necessary. ➢ During the treatment procedure, the recommended solution delivery rate is 1ml per minute. ➢ Once delivery is completed for the first syringe, if required by the physician for use, prepare the second 20 mL syringe of BioPearl (containing approximately 1 mL of drug-loaded microspheres) starting at Step 6.	➢ It is recommended to use a 1 mL luer-lock syringe for delivery for optimal pressure (sizes greater than 1 mL may increase chance of catheter blockages or increase in delivery pressure) ➢ Re-agitate microsphere suspension between the delivery syringe and suspension syringe a minimum of 5 times before each delivery. ➢ It is highly recommended to use a pulsatile delivery method for delivery. Non-pulsatile delivery may increase the likelihood of microsphere aggregation or catheter occlusion. ➢ It is recommended to flush the delivery catheter intermittently with saline between injections or after pauses in delivery for angiography. ➢ During the treatment procedure, ensure that BioPearl microspheres are still in suspension. Re-agitate suspension syringe as necessary. ➢ During the treatment procedure, the recommended solution delivery rate is 1ml per minute. ➢ Once delivery is completed for the first syringe, if required by the physician for use, prepare the second 20 mL syringe of BioPearl (containing approximately 1 mL of drug-loaded microspheres) starting at Step 6.

Loading Times per Vial of BioPearl™ Microspheres to Achieve 98% Loading Tolerance of ± 5%

	75mg Powder Doxorubicin per 2ml of embolic	75mg Liquid Doxorubicin per 2ml of embolic	50mg Epirubicin solution per 2ml of embolic	10mg Liquid Idarubicin solution per 2ml of embolic
Size (µm)	Time (hours)	Time (hours)	Time (hours)	Time (hours)
BP200	2	4	2	2

Recommended Non-Ionic Contrast Agents*

Product Name**	Active Ingredient	Iodine Concentration (mg/mL)
Omnipaque™, Accupaque™, Iohexagita®	iohexol	300
Ultravist®, Clarograf®, Proscope®	iopromide	300
Iomeron®, Imeron®	iomeprol	300

*Not provided or marketed by MicroVention.

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