



Sirtex Medical Limited

ABN 35 078 166 122

Level 33, 101 Miller Street
North Sydney NSW 2060

PO Box 6244

North Sydney NSW 2059

Phone: +61 2 9964 8400

Facsimile: +61 2 9964 8410

www.sirtex.com

30 August 2011

Dr Janice Campbell
William Beaumont Hospital
3601 W Thirteen Mile
Royal Oak, MI 48073
USA

Dear Dr Campbell,

Incident Report 778

We have received your incident report regarding Delivery Set used in SIR-Spheres[®] microspheres treatment on 27 April 2011. You reported that during administration of the spheres, forward flow stopped and back pressure was felt at the B-line syringe. We have received the returned goods and have evaluated them. We summarise the findings as follows:

Correspondence relating to this include your incident report direct from William Beaumont hospital (our ref #778), a verbal description of the event from NRC Chicago office and a letter from FDA following lodgement of an MDR by Beaumont. Attached to the returned goods was a copy of the report sent to NRC, for which we thank you.

We received back a fully attached used Sirtex Delivery Set, a used Sirtex V-Vial contained within a V-Vial Holder, with Line "D" of the delivery set in situ through the septum plus a Terumo brand microcatheter (labelled 2.8/130) which was attached to the A-line fitting of the Sirtex Delivery Set and a Terumo branded Tuohy-Borst Y-adaptor fitted over the catheter. These were wrapped in used drapes with other items associated with the procedure and the delivery apparatus (gloves, gauze, needle sheaths, Luer end caps). There were dried resin microspheres on the drapes plus the apparent remains of a SIR-Spheres microspheres dose contained within the Delivery Set and V-Vial, and. These were in an acrylic jar with a copy of the William Beaumont report as sent to the NRC attached to the outside.

The products were tested and a full report of the testing is attached. The conclusion was that high concentration of resin microspheres within the small internal diameter microcatheter is the likely root cause of the microcatheter occlusion occurring, aggravated by the use of a small syringe that would have had the effect of compacting the microspheres further.



Sirtex Medical Limited

ABN 35 078 166 122

Level 33, 101 Miller Street
North Sydney NSW 2060

PO Box 6244
North Sydney NSW 2059

Phone: +61 2 9964 8400

Facsimile: +61 2 9964 8410

www.sirtex.com

Your suggested approach to reducing a potential for a high concentration of microspheres to be present in the microcatheter, which is to divide the prescribed activity (dose) into two separate v-vials as stated in your own Beaumont report to the NRC is noted and we would concur. We would also make two other suggestions. The first is to ensure that the C-line needle is kept at the upper section of the vial as described in the set-up, where the concentration of microspheres is lower by gravity.

An associated approach that warrants consideration for prescribed activities within the higher range is that you may choose to only partially suspend the microspheres in the v-vial with water injected from the D-line, so that a very dilute suspension of microspheres passes into the C-line and thence into the 3-way stopcock then the A-line and microcatheter. This dilute aliquot loaded into the A-line can then be flushed with water from the B-line.

This technique may be applied to the first 3 – 4 aliquots of microspheres, when the microspheres in the v-vial are at their most concentrated.

We note the comment that you were unable to access assistance from us and can only apologise for that misunderstanding. Sirtex has expertise available should you wish to contact us through qa@sirtex.com or our US staff can facilitate such contact for you.

We found that the Terumo catheter flowed freely. It had a kink in it although this did not prevent free-flow and a likely possible cause of this would be from the way it was bundled post-procedure pending decay. We have forwarded these products to Terumo for its own evaluation as the manufacturer through the Australian Terumo subsidiary company.

If you would like further information regarding this product investigation, please do not hesitate to contact us.

Yours sincerely,

A handwritten signature in black ink, appearing to read "H Winslade".

Heather Winslade
Global Head of RA/QA
hwinslade@sirtex.com

cc: Dr M Savin – William Beaumont Hospital
Terry Hendricks, Regional Sales Manager, Sirtex Medical Inc
atts



Level 33, 101 Miller Street North Sydney NSW 2060 Australia
PO Box 6244 North Sydney NSW 2059

Incident Evaluation

Date: 11 August 2011

Ref: Incident Report 778

An incident report (#778) was received in April 2011, from Beaumont Hospital in MI, USA.

The incident report related that during administration of a SIR-Spheres microspheres dose, flow through the Delivery Set stopped and backpressure was felt at the B-line syringe. It was also reported that spheres were expelled from the end of the catheter upon its removal from the patient. The report specifically stated:

“After pressuring the v-vial and filling a portion of the A-line with spheres, after switching back to B-line flush and administering a sterile water push, forward flow stopped and backpressure was felt at the B-line syringe. A smaller syringe was attached and additional pressure was applied without forward flow. Procedure was stopped and catheter was removed from the patient. Upon removal, spheres were expelled from the end of the catheter, contaminating the sterile drapes.”

No batch codes of any devices were included in the incident report. The date of treatment was provided as 27 April 2011.

Return of the Delivery Apparatus to Sirtex was requested to allow evaluation of the delivery apparatus that was used, and potentially conclude the cause of this event.

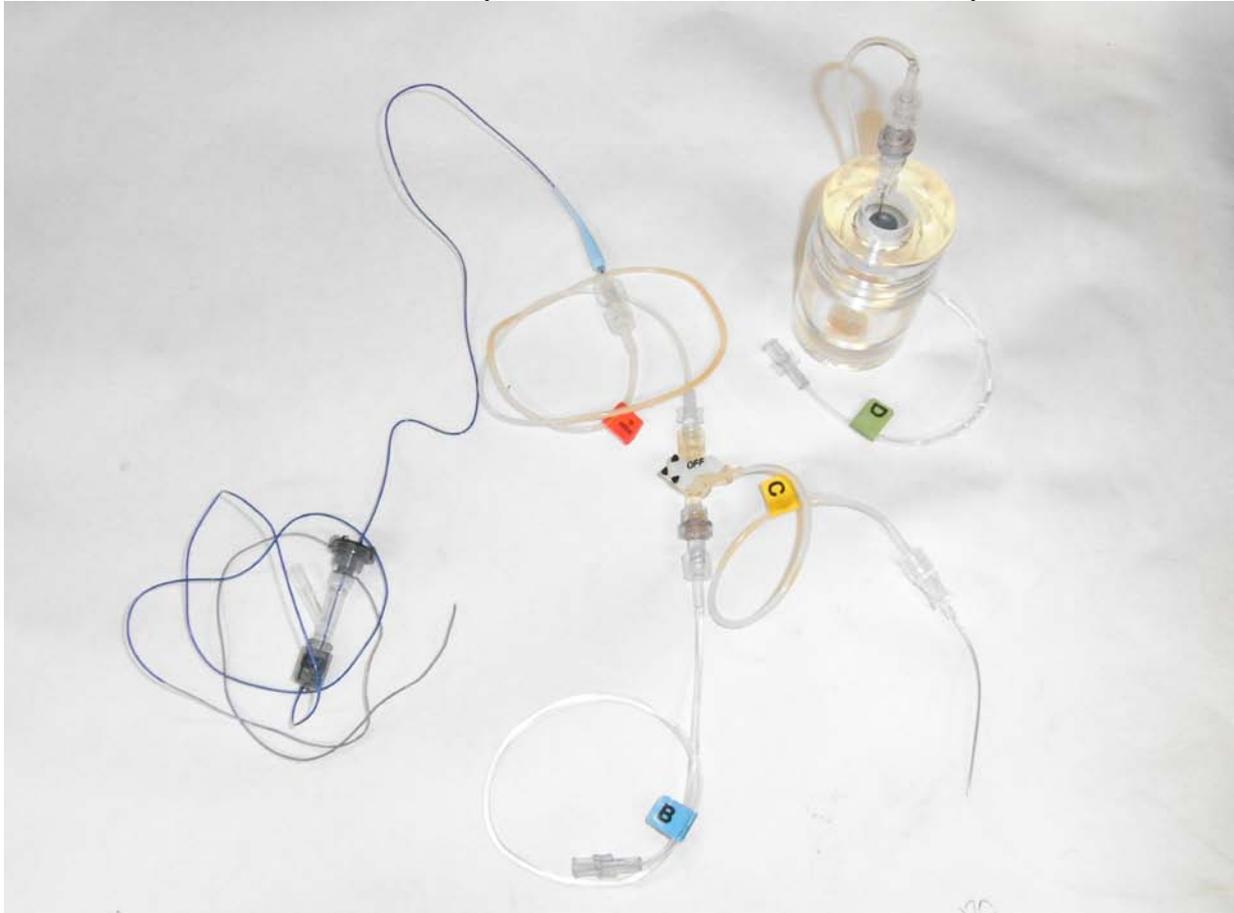
After suitable radioactive decay, the items were returned to Sirtex, and received at the Sydney office in August 2011, rolled up in surgical drapes and pushed tightly into a Nalgene 2 litre jar. The items were verified to have suitably decayed with no measurable residual radiation activity. The received jar was labelled, on the lid, with the following: “SIR-SPHERE occlusion Y-90 4-27-11 Device Failure”.

Items related to this incident, as returned included:

- A Sirtex Delivery Set,
- A Sirtex V-Vial contained within a V-Vial Holder, with Line “D” of the delivery set in situ through the septum,
- A Terumo brand catheter (2.8/130), attached to the A-line fitting of the Sirtex Delivery Set, also having a Terumo branded Tuohy-Borst valve fitted over the catheter,
- Drapes, plus other items associated with the procedure and the delivery apparatus (gloves, gauze, needle sheaths, Luer fitting end caps),
- Resin microsphere remains of a SIR-Spheres microspheres dose, contained within the Delivery set and V-Vial, and on the Drapes.

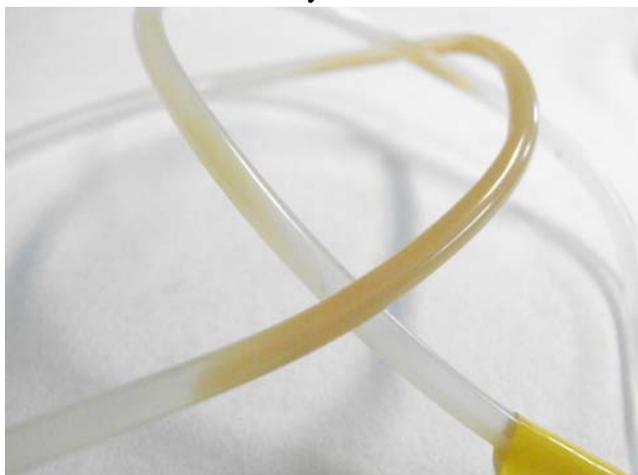
An initial inspection of all components was performed. As received, no caps were fitted to any of the open ends of delivery set lines or needles. No damage was noted to any parts upon initial inspection.

The returned items were still partly assembled (D-line inserted to V-vial septum, with V-Vial inside the V-Vial holder, and Delivery Set with catheter attached and Tuohy-Borst valve fitted).



The Delivery Set tubing and V-Vial were seen to contain resin microspheres. The V-Vial was observed to contain approximately 0.4ml volume of settled microspheres in the base of the vial, within 5ml of liquid.

Large concentrations of resin microspheres were easily visible inside the tubing of both “C” and “A” lines of the Delivery Set.



The stopcock assembly, connectors and valves of the Delivery Set were free of visibly concentrated microspheres. The stopcock valve rotated freely through all required positions. Some minor kinking in the Delivery Set tubing was observed, near the Luer fittings at the connection (catheter) end of the “A”-line, the stopcock end of the “B”-line, plus the needle end of the “D”-line. A minor kink was also present in the “A”-line tubing, approximately 150mm from the connection end.

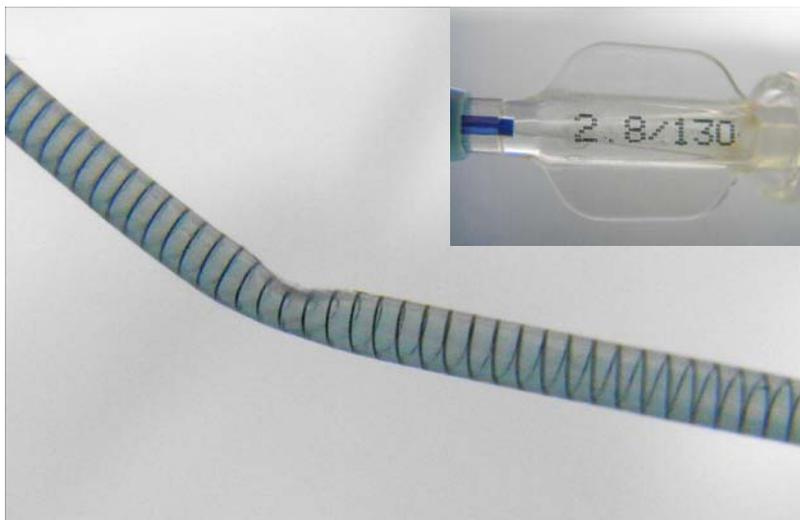
The stopcock valve was in the position “Off to C-line” when received, and open to the B to A line fluid path (Flushing Syringe to Catheter). The stopcock tap was tested and noted to rotate freely through all required positions and as required would not rotate beyond the intended stops.

All Delivery Set connections and components were inspected and found to be correctly assembled, fully engaged and securely bonded.



Tubing on all fittings was noted to be fully and correctly inserted.

Visual inspection of all Delivery Set, V-vial apparatus revealed no faults.



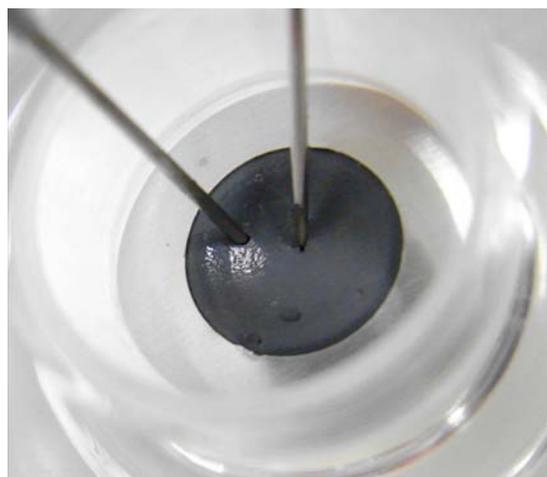
A single kink was observed in the Terumo catheter, approximately 240mm from the tip.

Functional Testing

The Delivery Apparatus was prepared for a functional test by re-introducing the “C”-line needle into the V-vial, using one of the existing needle punctures through the septum. The needles were positioned well above the remaining settled microspheres so no to disturb them at this time.

Two 30ml syringes (with water) were attached to the “B” and “D” line connections of the Delivery Set.

The end of the Terumo catheter was placed in a vial to collect any contents or internal residues.



The “B”-line was gently pressurised, and an easy flow was immediately established through the Delivery Set, with clear water leaving the catheter into the collection vial. No restriction was evident. The catheter was then disconnected from the Delivery Set “A”-line connection, and seen to drain freely into the collection vial with no pressure applied. A small quantity of water was then also flushed through the catheter, to collect any internal matter present in the collection vial. Neither before nor after a period to allow settling of any dispersed material were any residues or microspheres observed.

The contents of the “A”-line were then flushed, again easily with minimal pressure, to another vial to collect all the residual microspheres.



The stopcock was then rotated to allow the V-vial and C-line to be pressurised via the “D”-line using the connected syringe, and unobstructed flow was easily obtained, with minimal resistance. The remaining spheres in the base of the V-vial were quickly resuspended, and flow through the C-line and stopcock and to the open end of the A-line established. No clumps or blockages were seen.

The contents of the “A”-line and “C”-line were collected and after allowing the microspheres to settle, the volume was determined to be approximately 0.30ml of settled microspheres recovered from the Delivery Set lines.

The one-way valves that are fitted within the Delivery Set to ensure that reverse flow cannot occur were also verified to function as expected, that is admit flow in the forward direction only and prevent reverse flow.



Sections of the drapes were seen to have a concentrated residue of dried microspheres, evidently these were as expelled from the end of the catheter upon removal from the patient during the procedure. The most concentrated trail of microspheres was approximately 40mm in length, and represents a significant proportion of the SIR-Spheres microspheres dose, though the specific amount of microspheres present on the Drapes could not be determined with any degree of confidence.

A sample of the dried microspheres was taken from the drape, and placed into a vial of water to verify that they could be dispersed and resuspended. Although having been thoroughly dried on the drapes, the microspheres eventually rehydrated and were dispersed into suspension.

Conclusion

No blockage or occlusion of the Sirtex delivery apparatus or the Terumo catheter was observed or replicated.

The returned delivery apparatus performed as would be expected, both with and without the catheter attached. That is, there was free flow, with no restriction or excessive backpressure encountered during bench testing. The one-way valves were also verified to function as expected, therefore the reported *“backpressure was felt at the B-line syringe”* is believed to be describing resistance rather than backwards pressure felt at the syringe.

The reported blockage / occlusion was evidently cleared at the time of catheter removal, when the *“spheres were expelled from the end of the catheter”*.

The kinking noticed in the Delivery Set tubing was not likely to have been causal to the reported blockage. The kinking is possibly due to the packaging of the items for return, and it is probable that kinks occurred after the event, during packing, decay storage and shipping, compressed in the 2 litre Nalgene jar. Even with the noted kinks present during the functional testing, these did not impede the flow of fluid and suspended microspheres.

The amount of microspheres reclaimed from the Delivery Set tubing suggests that the reported blockage was caused by too high a concentration of microspheres being admitted to the delivery set and catheter, with inadequate flushing of the delivery system to keep the microspheres suspended and flowing, causing the catheter to become clogged. This conclusion is reached because the total amount of microspheres reclaimed from the Delivery Set “A” and “C” lines amounts to approximately 28% of the entire dose being present in the Delivery Set at the one time, in addition to the unquantifiable amount of microspheres that were expelled from the end of the catheter upon its removal from the patient during the procedure.

The switching to a smaller than recommended syringe (from incident report related by the user: “A smaller syringe was attached and additional pressure was applied without forward flow”) would have compounded and compressed the blockage in the catheter, and caused a further build-up of pressure leading to the expulsion of the string of spheres on removal of the catheter from the patient. The actual expulsion of the microspheres would likely have occurred due to the reduction of backpressure that is present at the end of the catheter whilst it is in situ, therefore increasing relative pressure behind the obstruction in the catheter, together with flexing associated with the movement of the catheter allowing disturbance and dislodgement of the plug of compressed microspheres.

It is unclear and cannot be determined whether the kink observed near the end of the Terumo catheter was present at the time of the administration. The kink was not found to obstruct the flow of liquid through the catheter, and although on its own not likely to be causal of the blockage reported, it could have contributed by serving as a starting point to the collection of microspheres, if it was presented with a high concentration of microspheres as were evidently present.

*Erik Strautnieks
Global Quality Manager
Sirtex
11 August 2011*

End of Document