Microbial Safety Assessment of a Double Check-Valve Patient Line in a Multiuse Contrast Delivery System

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Purpose To demonstrate the microbial safety of a secure filling and injection kit designed to allow for multiple injections of contrast media from a single large-volume container in computed tomography (CT) and magnetic resonance (MR) imaging examinations.

Methods Two male *Papio anubis* baboons were injected with technetium-99 labeled albumin to mimic a contaminated patient. Researchers injected iodinated contrast medium into the animals using an automated power injector via an antecubital vein, with an injection line fitted with a double check-valve positioned at a 45° angle toward the vein (worst-case condition). Two contact times (before and after injection) were assessed in 3 experiments and repeated 3 times for a total of 9 tested lines. Radioactivity levels were measured in the animals' plasma and in the injection system.

Results Crude values were corrected for background signal and technetium Tc 99m radioactive decay. Results showed an absence of contamination in the line above the check-valve. Negative results were because the mean value of background noise was similar to the crude values measured.

Discussion Injecting contrast media from a large-volume container decreases the cost of CT and MR examinations. However, this practice, which involves the use of the same injection system for multiple patients, is associated with a risk of cross-contamination and requires manufacturers to demonstrate the safety of reusable injection kits.

Conclusion Based on appropriate demonstration of worst-case conditions and the use of a radiolabeled molecule mimicking a pathogen particle (ie, as small as viral particles), this study highlights the safety and performance of the tested injection system to perform repeated injections from a multidose container to more than one patient, regardless of the conditions and duration of the examination.

Automated contrast media injections are required in approximately 40% to 60% of computed tomography (CT) scans and 30% of magnetic resonance (MR) imaging procedures.[1] Because of the risks of nosocomial infection associated with gravity infusion and power injection, single-use bottles of contrast media, tubing, and other supplies are recommended.[2] However, as a result of increased use and the high cost of contrast media, disposable material constitutes a chief financial burden for medical imaging centers.[3-5] To decrease costs, as well as improve CT room workflow and minimize radiographer handling error, contrast media sometimes are injected into several patients from the same container.[6] Large-volume contrast media containers (vials or prefilled soft bags) permit multiple administrations. Almost all iodinated contrast media manufacturers offer containers with a larger volume ($\leq$ 500 mL) than one required for a single patient (usually $\leq$ 100 mL). The growing use of this practice is supported by improved handling conditions, especially injection materials and aseptic procedures. However, the cost savings related to multiuse practices must be considered in conjunction with the risk of cross-contamination between patients.

Literature Review

According to the literature, the risk of bacterial, parasitic, or viral infection associated with radiologic examinations is low; nevertheless, the risk exists and

must be taken into account.[7-11] One study reported malaria infection in 6 cases attributed to a power failure that shut down injection, possibly causing reflux into an injection line not equipped with an antireflux valve.[12] Other case reports highlight failure to comply with aseptic procedures as the reason for these incidents.[13-16]

In May 2008, 5 cases of hepatitis C virus infection were reported after cardiac imaging. It was suspected that these were caused by the inappropriate use of a bottle of physiological saline solution, although this could not be proved. The study highlighted the importance of using syringes and needles only once to avoid the risk of cross-contamination when using one bottle.[13]

From August through November 2004, 6 cases of hepatitis C were identified following CT scan in 3 centers in Spain. Blood contamination was possible in all 3 centers via the personnel who, in order to change the extension tubes, disconnected the tube from the patient first and then from the equipment without changing gloves between these manipulations.[14] An October 2004 investigation identified an acute hepatitis C virus infection outbreak identified among patients who underwent myocardial perfusion studies. The investigation concluded that the practices at the pharmacy could have facilitated breaks in aseptic technique.[15]

On February 19, 2003, 4 cases of contamination with *Klebsiella oxytoca* were reported following injections made during intracranial nuclear MR examinations. It was reported that the physiological saline solution used to flush tubing before the injection of contrast media was from one insufficiently sterilized bottle.[16]

Cases of infection related to the use of multiuse contrast delivery systems reported in the literature have led the studies' authors to implicate the absence of antireflux valves, inappropriate disconnecting procedures, and noncompliance with required aseptic procedures as potential causes of infection.[12-16]

Recommendations to reduce contamination risk related to multidose containers include strict compliance with aseptic techniques, use of all materials within 8 hours, and adherence to multi-injection protocols. These protocols include following the correct disconnection sequence and using patient lines fitted with 2 antireflux valves that must be changed between each patient.[4] Injection tubing manufacturers are required to demonstrate the effectiveness of the antireflux valves and the bacterial safety of multiuse injection systems. However, few studies have been done, and clinical relevance is sometimes doubtful in the existing studies because they do not reflect clinical reality or worst-case scenarios. For example, Cona et al evaluated the performance and safety of a multiuse injection system in relation to the risk of back-contamination[17]; this study was conducted on rabbits, did not simulate clinical human conditions, and did not include worst-case conditions. Moreover, radioactivity counts were not evaluated with respect to a potential viral load, and the bias related to possible absorption of radioactive elements into the plastic tubing was not taken into account.

Purpose

The aim of this study was to investigate the biological safety, under clinical worst-case conditions, of a patient delivery system designed to allow for multiple safe injections from a single-use multidose container. The tested system comprised a combination of 2 commercially available devices, manyfill (Medex) and secufill (Medex). The manyfill is a filling and injection system connected to the injector. The secufill is a patient line with a double check-valve connected between the manyfill and the patient. The secufill patient line is changed between each patient, while the manyfill system can be used for up to 8 hours when complying with device instructions.

The secufill check-valve is equipped with 2 silicone mechanical components that permit fluid to flow in one direction. It is characterized by its opening pressure being lower than the valve opening pressure, thereby preventing injection and backflow of blood into the injector line.[18] Silicone diaphragms of check-valves typically are closed, and their opening and closing are directly related to a positive cut-off upstream/downstream differential pressure. Valve safety is directly related to a short closure time.

This nonclinical study was conducted in 3 steps. The first step involved investigating the reproducibility of the performances of the double check-valve by in vitro characterization of valve parameters (opening pressure parameters and closure time) and assessing the influence of the viscosity of the injected solution

(contrast medium or saline). In the second step, an in vitro backflow test using blue dye defined the clinical worst-case conditions that would expose patients to a risk of back-contamination due to blood backflow. Last, in an in vivo study performed in baboons, the risk of back-contamination of the delivery system was assessed under the previously defined clinical worst-case conditions.

Materials and Methods

Test 1

This experiment was conducted to assess secufill valve parameters following automated injections of either iodinated contrast medium or standard saline solution for CT (see **Figure 1**). The aim of this test was to qualify the secufill line and valve and determine the impact of the injected product on valve function. Four batches of silicone and 2 manufacturing processes were compared. Statistical tests were performed by Medex in Excel (Microsoft); significance was determined by a *t*-test and coefficients of variation. Two separate automated power injectors, ADDIX (Medex) and Dual Shot Alpha (Nemoto Kyorindo Co Ltd), were used to eliminate biases linked to injector parameters. The parameters studied were the time to complete closure of the diaphragm and the pressure differential between the 2 sides of the system. The effect of repeated injections on the valve and the impact of the fluid on time-to-closure and pressure differential also were examined. A total of 100 valves were tested in various configurations (see **Table 1**).

Test 2

The objective of this second test was to identify the worst-case clinical conditions associated with a risk of back-contamination due to blood backflow in the line. The test consisted of identifying parameters that influence backflow of Patent Blue V (Guerbet) through the secufill: the nature of the product in contact with blood according to its viscosity (contrast medium or saline), the position of the connection of the patient line to the venous access, and the contact time (see **Figure 2**). Backflow was defined as diffusion of the blue dye from the distal end of the secufill (patient side) to the other side of the valve (injector side), thus mimicking back-contamination from a patient to fluid containers (syringes, in most cases).

First, 2 solutions, a saline solution and a contrast medium solution (iobitridol 350 mgI/mL; viscosity 21 mPa·s at 20°C and 10 mPa·s at 37°C) were tested. Each solution was tested in combination with 2 secufill positions (−45° or 45°) in relation to the connection point (6 for each solution and position for a total of 12 for each solution). Each test was repeated 3 times (18 samples for each solution). Then 2 solution contact times (5 min or 30 min) were tested for only the contrast medium solution in only one position (45°), and

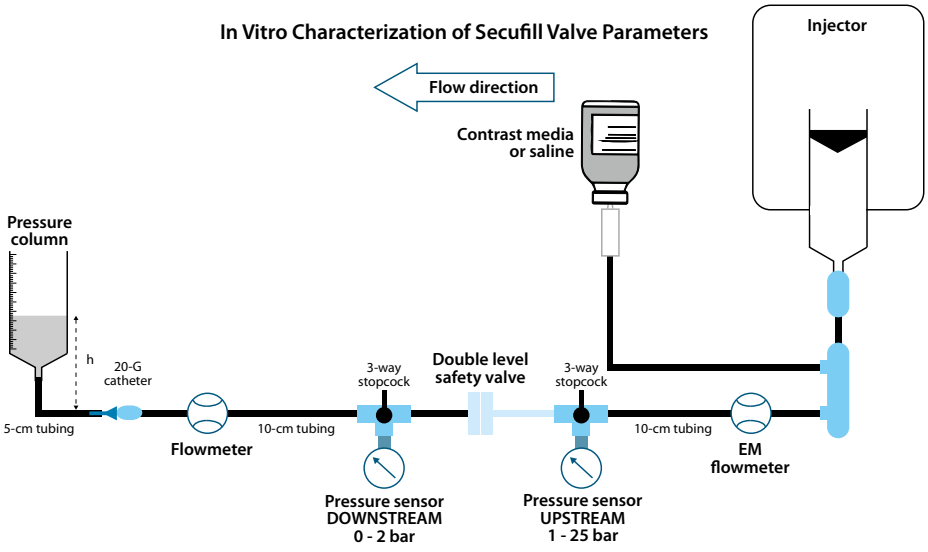

Figure 1. *The set-up was prepared to measure pressure and flow upstream and downstream to the secufill valve under conditions mimicking clinical conditions. The upstream line was connected to the injector, and a back pressure of 10 mmHg was applied to the downstream line with an appropriately prefilled column. This back pressure was applied to mimic human intravascular pressure.*

Table 1

In Vitro Characterization of Secufill Valve Parmeters: Configurations Tested

	Injector and Tested Solution			
	Dual Shot Alpha Injector (Nemoto Kyorindo Co Ltd)		ADDIX Injector (Medex)	
Batch	Standard Saline Solution	Iodinated Contrast Medium	Standard Saline Solution	Iodinated Contrast Medium
A (silicone lot)	x	x		
B (silicone lot)	x	x	x	x
C (silicone lot)	x	x		
D (manufacturing process)			x	x

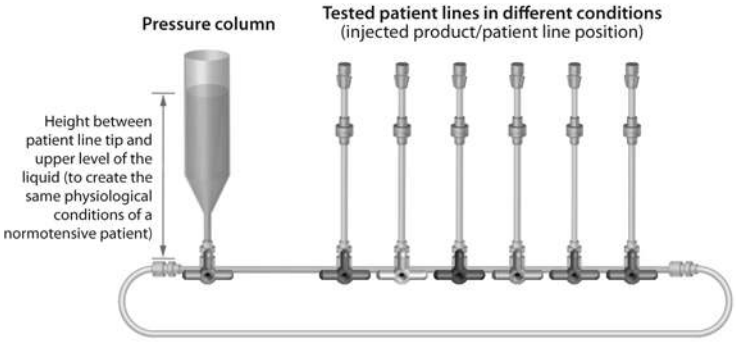

Figure 2. *The set-up was prepared to compare 6 secufill devices connected in series to 6 stopcocks on an infusion manifold. Before connecting and filling the secufill lines, a back pressure of 10 mmHg was applied throughout the system with the use of an appropriately prefilled column connected upstream to the manifold. This back pressure was applied to mimic normotensive patient intravascular pressure.*

the test was repeated 4 times (24 samples). Patent Blue V solution was chosen as it has similar osmolarity as blood, and it can be measured easily by spectrophotometry at a wavelength of 640 nm because of staining caused by diffusion of the solution. The Beer-Lambert law was applied to determine Patent Blue V concentrations. A total of 96 secufill valves were tested in various configurations (see **Table 2**).

In Vivo Preclinical Study

A pilot study and a complementary study were performed at the French Alternative Energies and Atomic Energy Commission (*Commissariat à l'Energie Atomique et aux Energies Alternatives* [CEA]) after approval by the CEA institutional ethics committee (see **Figure 3**). All experimental procedures were performed in accordance with French regulations and in compliance with the European Economic Community Directive (2010/63/EU) on animal welfare. Statistical means and standard deviations were calculated using Excel. Two male *Papio anubis* primates weighing 21.5 kg and 25 kg were included. One of the animals was included in both the pilot study and the complementary study, while the other animal was included only in the complementary study. In both studies, the animals were anesthetized by intramuscular administration of 1 mg/kg of ketamine hydrochloride and 5 mg/kg of 2% xylazine hydrochloride. Each animal was sedated for a maximum of 3 hours with the use of 10 mg/mL of propofol at 3.5 mg/kg/h, injected through a dedicated 3-way stopcock connected to a catheter introduced into an antecubital vein. Each animal was intubated and ventilated throughout the experiments. Thermoregulation was maintained with a warming air pad system to limit the decrease in body temperature caused by anesthesia. Blood pressure was monitored with blood pressure cuffs, and physiological parameters (respiratory frequency, oxygen saturation pCO_2, body temperature, and arm blood pressure) of the anesthetized primates were controlled throughout the study. On completion of the experiment, animals woke under supervision before being transferred to their facilities.

A single dose of 220 MBq of technetium Tc 99m albumin was prepared extemporaneously according to the manufacturer's recommendations. Quality control tests were performed for each synthesized batch proving the absence of free pertechnetate in the final

Table 2

In Vitro Diffusion Tests of a Patent Blue V Solution in Saline or Iodinated Contrast Medium Solutions at 21°C

Solution	Angle	Time (min)	No. Lines × No. tests
Saline	45°	5	6 × 3
		30	
	−45°	5	6 × 3
		30	
Contrast medium	45°	5	6 × 3
		30	6 × 4
	−45°	5	6 × 3
		30	

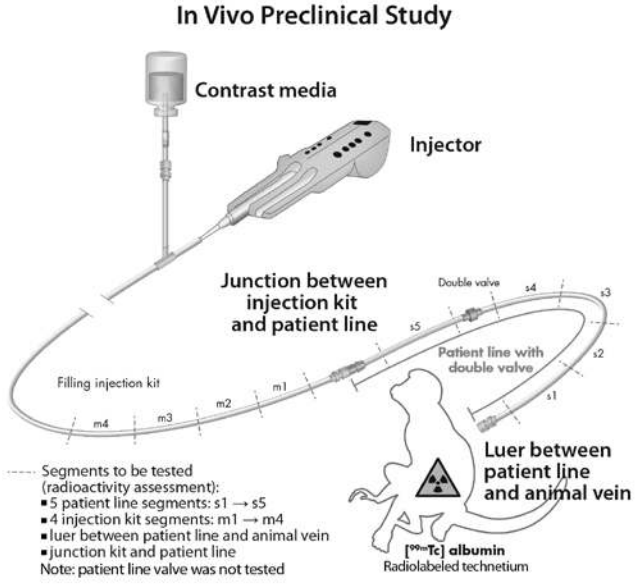

Figure 3. *The primates were injected with contrast media, and the secufill was connected to the primate arm at a 45° angle from the venous access. These conditions have the highest risk of blood backflow. Two experiments, a pilot study and its complementary study, were performed to assess 2 criteria: the contact time after the connection of the secufill line and animal vein before the injection, and the lapse time before disconnecting the secufill line from the animal after the injection.*

ready-to-inject preparations. Technetium Tc 99m albumin (5 mL, 48 MBq/mL) was administered to the animals through the calf venous access. Every 15 minutes, a 1 mL sample of arterial blood was drawn to monitor plasma radiotracer concentrations over time on 200 μL of plasma to assess natural blood clearance of the radiopharmaceutical.

To simulate a typical clinical setting, studies were performed with an automated power injector, Dual Shot Alpha, and the contrast medium was injected via the antecubital venous access. The manyfill line was connected to the injector. One of the 2 syringes was filled with iobitridol using the manyfill filling and injection line.

Researchers chose the iodinated contrast medium instead of saline on the basis of conclusions from the previous in vitro diffusion tests of a Patent Blue V solution in saline or iodinated contrast medium solution that identified that the worst-case clinical conditions associated with a risk of blood backflow is higher when blood comes in contact with contrast medium as opposed to contact with saline. For each animal, the secufill line was then connected to the manyfill injection line and the entire injection system was purged of contrast medium. The patency of the animals' venous access was checked by a preliminary saline flush before connecting the secufill through a short 22-gauge radiopaque IV catheter (Jelco, reference 4030, length 25 mm, diameter 0.9 mm). This catheter was closed between injections with a 22-gauge obturator (Jelco, reference 4022, length 25 mm). The secufill line was configured according to the conclusion of the previous worst-case studies that showed that the risk of blood backflow was higher when the secufill line was positioned at a 45° angle from the venous access. This condition was applied to all in vivo experiments.

In the pilot study, contrast medium was injected 2 minutes after connecting the secufill line to the vein. Iobitridol (10 mL) was injected at a rate of 2 mL/s. A 30-minute contact time was observed before disconnecting the secufill line from the animal's vein. The complementary studies consisted of applying the same protocol in 2 animals under 2 different conditions,

complementary study A and complementary study B (see **Table 3**). Contact times before injection were 15 minutes for A and 2 minutes for B; contact times after injection were 30 minutes for the CT scan in A and 60 minutes for the MR scan in B. Each experiment was performed in triplicate for each animal, resulting in a total of 3 results for the pilot study and 6 results for the complementary studies. Nine secufill lines were used for these 3 experiments.

The lines were disconnected from the catheter after the predefined contact times, and the radioactivity associated with the lines was determined. To limit biases in radiometer counts due to radiopharmaceutical absorption onto the plastics, the entire secufill line and only the distal segment of the manyfill line containing contrast medium were immediately frozen in dry ice before being cut into fragments for analysis. The distal part of the manyfill line was cut into four 3-cm segments (m1-m4). The secufill line was cut into five 2.7-cm segments: 4 segments in the distal line (s1-s4) and 1 segment above the check-valve (s5). The luer locks between the secufill and the animal's vein and between the secufill and the manyfill also were sampled. These 11 samples were weighed to express radioactivity counts per unit weight (see **Table 4**). Radioactivity of plasma samples and frozen samples was determined with a Cobra II system (Hewlett Packard) using gamma ray detection between 15 kiloelectron volts (keV) and 2000 keV for 60 seconds, and values in cut samples were expressed in counts per minute per gram of blood (cpm/g).

Table 3

In Vivo Preclinical Study: Configurations Tested

Study	Contact Time After Connection of Secufill Line to Vein in Min (before injection)	Contact Time Before Disconnecting Secufill Line From Animal Vein in Min
Pilot study	2	30
Complementary study A	15	30
Complementary study B	2	60

Radioactivity levels in primate plasma were measured every 15 minutes to assess radiopharmaceutical blood clearance. The background noise of the device also was assessed 3 times with the use of empty hemolysis tubes, or tubes containing a segment of line not previously exposed to radioactivity, and a small volume of iobitridol. Both the background noise and the technetium Tc 99m radioisotope half-life (6 hours) were taken into account to normalize the values.

Background noise was subtracted from the count values of the various samples to determine the true radioactivity in the sample. The values obtained then were corrected from technetium Tc 99m decay over time to allow for direct comparison of the final values regardless of the sampling time.

Results

Test 1

The results of in vitro characterization of the secufill valve opening pressure and parameters are as follows:

- The batches of silicone used for manufacture of the valve had a limited impact on the pressure differential required for valve closure and no impact on time-to-closure.
- As expected, time-to-closure of the valve was longer following contrast medium injection than following saline injection because of the different viscosities of the 2 solutions, indicating that contrast medium constituted the worst-case condition.
- Repeated injection had no impact on these parameters.
- No significant variation of the results was observed according to the power injectors used.
- Valves obtained by different manufacturing processes gave similar results.

Test 2

The results of in vitro backflow tests of Patent Blue V in saline or iodinated contrast medium solutions were used to define the worst-case conditions to mimic blood backflow:

- The longer the valve made contact with the blue solution, the more the blue solution diffused throughout the line (see **Figure 4**).
- Backflow was more marked with iodinated

Table 4

Measurement of Radioactivity in the Baboon Blood and in the Device in cpm/g[a]

Double Check-Valve Patient Line (proximal to double check-valve)	Pilot Study[b]		Complementary Study A[c]		Complementary Study B[d]	
	Mean	SD	Mean	SD	Mean	SD
Luer	8262	8681	18180	9518	10153	6929
s1	2201	1630	4297	3137	3141	3546
s2	1945	1132	5307	4130	3296	2965
s3	1994	1095	4997	3825	3671	3120
s4	1699	1050	4041	3114	3420	3570
Double Check-Valve Patient Line (distal to double check-valve)						
s5	21	50	−28	19	−53	13
Junction	21	34	4	2	−8	25
Injection Line (distal to double check-valve)						
m1	7	49	−37	47	−86	121
m2	20	39	−25	42	−52	42
m3	20	10	−23	34	−44	39
m4	28	41	−32	57	−12	40

[a]*Values are corrected for background noise and decay of the radioisotope.*

[b]*Contact time after connecting patient line to animal vein before injection: 2 min. Contact time before disconnecting patient line from animal vein after injection: 30 min.*

[c]*Contact time after connecting patient line to animal vein before injection: 15 min. Contact time before disconnecting patient line from animal vein after injection: 30 min.*

[d]*Contact time after connecting patient line to animal vein before injection: 2 min. Contact time before disconnecting patient line from animal vein after injection: 60 min.*

Abbreviations: cpm/g, counts per minute per gram of blood; m, manyfill; s, secufill; SD, standard deviation.

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contrast medium injection than with saline.

- An angle of 45° with the secufill resulted in more marked backflow (see **Figure 5**).

In Vivo Experiments

Laboratory parameters analyzed during the in vivo studies demonstrated that the 2 baboons tolerated all experimental procedures, including sedation, anesthesia, catheterizations, radiopharmaceutical injection, iodinated contrast medium injection, and multiple blood samples for 3 hours in each protocol, and recovered a normal status following the experiments (see **Table 5**).

The mean radioactivity in the baboons' plasma at the end of the contact time for the 3 experiments was 7 340 937 ± 2 374 843 cpm/g of plasma (n = 3). Mean radioactivity measured on the patient side of the patient line just before the double check-valve was 3054 ± 2644 cpm/g (n = 9). In comparison, mean radioactivity measured in the patient line beyond the double check-valve was −20 ± 43 cpm/g (n = 9), and in the injection line it was −38 ± 80 cpm/g (n = 9). The radioactivity measured during the pilot study demonstrated the absence of contamination of the secufill segment above the valve (mean corrected radioactivity in segment 5 of the

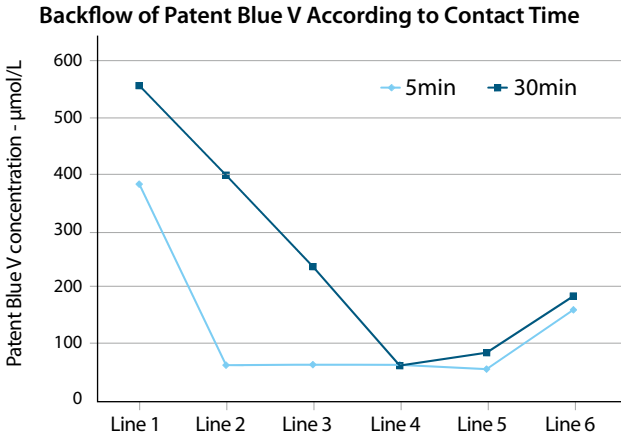

Figure 4. *For each line of 6 samples tested, the colored solution diffused more when the contact time is 10 minutes (compared with 5 minutes).*

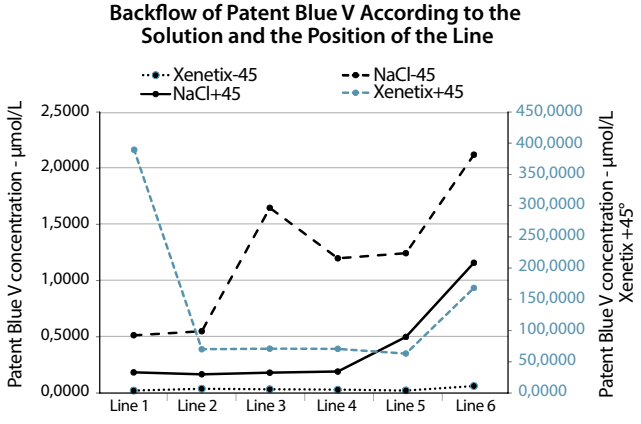

Figure 5. *For each line of 6 samples tested, backflow was more marked when the iodinated contrast medium (compared with saline) was injected at an angle of 45° to the secufill.*

secufill: 21 ± 50 cpm/g; n = 3) and in the manyfill line (mean corrected radioactivity in segment 1 of the manyfill: 7 ± 49 cpm/g; n = 3) (see **Figure 6**). The complementary studies confirmed these observations (n = 6) and demonstrated that contact times between lines before (2 and 15 mins) and after (30 and 60 mins) contrast medium injection did not modify the range of radioactivity values measured proximal and distal to the valve, as illustrated in **Figure 7**. Standard deviations reported for each sample were calculated from triplicate experiments.

Table 5

Baboon Plasma Radioactivity Values at Start and End of Experimental Time in cpm/g[a]

	Pilot Study	Complementary Study A	Complementary Study B
Start time	8 435 593	9 427 908	11 562 924
End time	7 458 922	4 909 300	9 654 589

[a] *Values are corrected for background noise and decay of the radioisotope.*
Abbreviation: cpm/g, counts per minute per gram of blood.

Radioactivity expressed in cpm/g in the distal part of the secufill was sometimes negative (see Table 4). The crude values measured by the gamma counting system after correction for natural decay and background noise were similar, and the mean background noise was sometimes higher than the sample values, resulting in a negative result. This observation confirms the absence of radioactivity in the distal part of the secufill beyond the valve.

Discussion

Reducing contamination risks of multidose containers to an acceptable level requires compliance with aseptic technique, the use of all materials within 8 hours, an appropriate disconnection sequence, use of the devices according to their intended use, and safe injection protocols using a single-use double check-valve injection system for each patient.[2,4,19,20] The safety of the multiuse procedure depends on the technique of the health care professionals who perform the injections, as well as on the safety of the multiuse delivery system. Because demonstration of the safety of these delivery systems is not defined by any standards, it is the manufacturer's responsibility to demonstrate safety.

Such safety testing must be conducted under conditions reproducing clinical conditions as closely as possible and under worst-case conditions associated with maximum contamination risks. The conditions associated with maximum contamination risks must first be identified, particularly the conditions resulting in the longest valve-closing time. The clinical conditions associated with the highest contamination risks, such as a maximum risk of backflow of the patient's blood into the injection line, also must be taken into account.

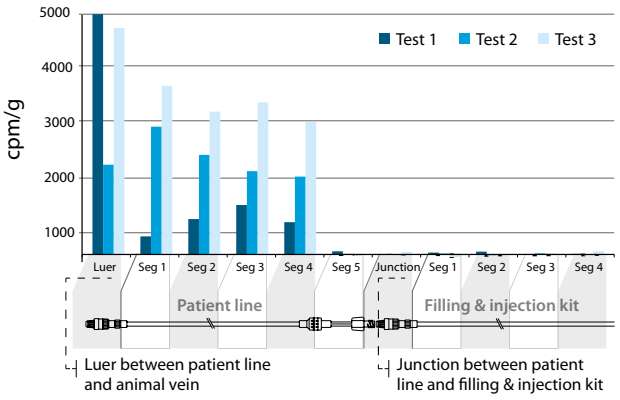

Figure 6. *Radioactivity measurements (cpm/g) of 11 distinct pieces of the injection system (secufill and distal part of the manyfill line): triplicate results (test 1, test 2, and test 3) in one animal. Truncated value for "luer security" test 1 = 14485 cpm/g.*

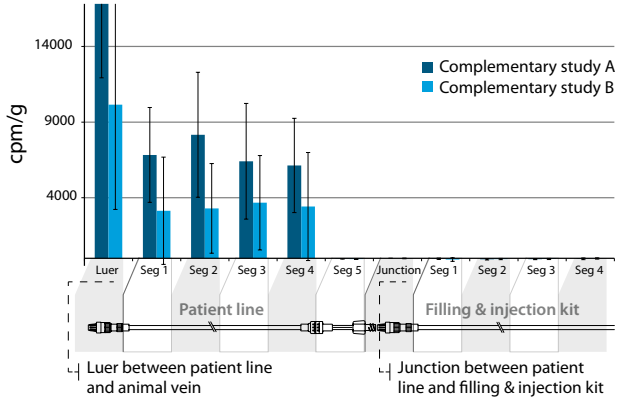

Figure 7. *Radioactivity measurements (cpm/g) of 11 distinct weighed pieces of the injection system (mean results of triplicate tests for complementary studies A and B).*

Safety testing should use the worst-case contaminant, or an element representing this contaminant, to simulate contamination by a number of small diffusible molecules such as viruses comparable to that of virus-contaminated blood. Simulation of contamination is a difficult exercise; apart from studies of bacterial contamination, only a few preclinical and clinical studies have evaluated the risk of contamination with viral particles or small diffusible molecules.[13]

In this study, worst-case conditions were defined in 2 stages. A first in vitro study (test 1) evaluated valve function according to certain criteria and demonstrated that contrast medium had a higher risk of backflow than saline because the valve-closing rate was significantly longer with contrast medium. A second in vitro diffusion study with a blue dye (test 2, allowing for diffusion determination by visual inspection or spectrophotometry measurement) permitted the definition of worst-case clinical conditions. The physical position of the secufill in relation to the venous access (45° angle) was shown to be a critical parameter in the in vivo experiments. The 45° angle between the secufill and the venous access was associated with an increased risk of viral contamination because of the viscosity difference between blood and the contrast medium.

This study also confirmed that contact time must be taken into account and that the highest risk of contamination of the system occurred with the contrast medium rather than with saline as a result of more marked diffusion of the Patent Blue V solution, which has similar osmolarity to that of blood. The limitation of these in vitro observations is that extrapolation of blue dye concentrations proximal to the secufill valve is not clinically relevant because the molecular weight of Patent Blue V is not comparable to that of blood cells, the viscosity and diffusion properties of the tested fluids are different from those of blood, and the limit of detection of spectrophotometry (8.10^{-7} M) does not allow for accurate and sensitive measurements proximal to the secufill valve.

In this context, experiments were performed using nonhuman primates and a radiopharmaceutical to reproduce clinical conditions and obtain higher sensitivities. Animals were placed in a supine position, and contrast medium was injected into an antecubital vein to simulate clinical conditions. To mimic worst-case clinical conditions for the in vivo study, contrast medium, rather than saline, was injected at a 45° angle between the secufill and the venous access, after contamination by technetium Tc 99m albumin. The use of this radiopharmaceutical was justified by the nature and, more importantly, the size of this molecule: It is a highly soluble protein with a diameter of 3.6 nm, which is smaller than the viral contaminants typically tested, such as minute mice virus (18-26 nm) and poliovirus (20 nm), and is therefore a worst-case diffusible molecule.

In the in vivo study, primates were injected intravenously with a mean dose of 9.9 ± 0.8 MBq/kg of body weight using freshly prepared technetium Tc 99m albumin solution. The quantity of radiolabeled albumin injected is equivalent in terms of number of molecules to a viral load of approximately 1.10^9 particles per mL of blood. This dose was defined to be representative of a viral infection. Visual observations during the pilot study showed blood flowed into the proximal part of the secufill when it was connected to the patient's catheter. The presence of blood close to the valve was identified as the main risk for backflow contamination; therefore, 2 contact times before injection were tested in the complementary studies. In addition to these 2 contact times, 2 more contact times after injection were tested to mimic real examination times: a 30-minute contact time for CT and a 60-minute contact time for MR imaging examinations.

To ensure more reliable radioactivity measurements, all crude radioactivity counts were corrected for background noise and decay of the radioisotope. The biological plasma half-life of labeled albumin, measured by counting plasma radioactivity every 15 minutes, was estimated to be 3 hours. This time period is long enough to permit a slight variation of the plasma concentration of technetium Tc 99m albumin during the experiment, thereby allowing for extrapolation of the quantity of radiolabeled albumin to a stable viral load. Clearance of the radiopharmaceutical was calculated for the 2 primates and ranged from 3 hours to 12 hours. To limit biases possibly due to radiopharmaceutical absorption onto the plastic lines, the whole secufill line and the distal part of the manyfill line containing contrast medium were immediately frozen in dry ice before being cut into fragments for analysis. The design of the in vivo study, taking all of these parameters into account, ensured the reliability of the method and results as well as the performance of the device in worst-case clinical conditions despite the small number of animal experiments.

A study previously published by Cona et al also evaluated the performance and safety of a multiuse injection system in relation to the risk of back-contamination.[17] They found their tested delivery system allowed the contrast injection system to be used multiple times without risk of cross-contamination. However, their study did not take into account worst-case conditions and did not simulate clinical human conditions, among other limitations.

Conclusion

This study, based on in vitro characterization of the secufill check valve and appropriate demonstration of clinical worst-case conditions of power injections in medical imaging, provides a reliable demonstration of the performance and safety of the secufill valve in terms of the risk of contamination due to blood backflow. The results of the in vivo preclinical study performed in baboons with the use of a radiolabeled molecule mimicking a pathogen particle demonstrate the impermeability of the double check-valve even in worst-case conditions. The combination of the secufill single-use patient line and appropriate tubing for automated power contrast medium injection allows for multiple injections with no risk of cross-contamination between patients provided the manufacturer's recommendations, handling procedures, and aseptic conditions are observed.

In the future, this type of study might lead to official guidelines for the use of multiuse materials, such as bottles of contrast medium and tubing, by helping medical imaging centers improve the workflow in a CT room, minimize handling errors for radiographers, and reduce operating costs.

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References

1. Ma X, Singh A, Fay J, Boland G, Sahani DV. Comparison of dual-syringe and syringeless power injectors in outpatient MDCT practice: impact on the operator's performance, CT workflow, and operation cost. *J Am Coll Radiol*. 2012;9:578-582. doi:10.1016/j.jacr.2012.04.007.
2. Siegel JD, Rhinehart E, Jackson M, Chiarello L; Health Infection Control Practices Advisory Committee. 2007 guideline for isolation precautions: preventing transmission of infectious agents in health care settings. *Am J Infect Control*. 2007;35(10)(suppl 2):S65-S164. doi:10.1016/j.ajic.2007.10.007.
3. Beussink DR, Godat JF, Seaton T. Antimicrobial properties of magnetic resonance imaging contrast media. *Am J Health Syst Pharm*. 2000;57(1):48-50.
4. Cantin V, Labadie R, Rhainds M, Simard C; for L' Unité d'évaluation des technologies et des modes d'intervention en santé du Centre Hospitalier Universitaire de Québec. L'administration intraveineuse des substances de contraste en imagerie médicale au CHUQ. http://www.chuq.qc.ca/NR/rdonlyres/30F16456-0DF4-474B-B657-1176948AAA94/0/rapport_substance_contraste.pdf. Published May 14, 2007. Accessed September 9, 2015,
5. Buerke B, Puesken M, Mellmann A, Seifarth H, Heindel W, Wessling J. Microbiologic contamination and time efficiency of use of automatic MDCT injectors with prefilled syringes: results of a clinical investigation. *AJR Am J Roentgenol*. 2010;194(2):299-303. doi:10.2214/AJR.09.3189.
6. Routhier J, Piazzo K, Sodickson A. Contrast and cost savings by implementation of a multidose bulk IV contrast delivery system. *J Am Coll Radiol*. 2011;8(4):265-270. doi:10.1016/j.jacr.2010.08.031.
7. Longfield R, Longfield J, Smith LP, Hyams KC, Strohmer ME. Multidose medication vial sterility: an in-use study and a review of the literature. *Infect Control*. 1984;5(4):165-169.
8. Mattner F, Gastmeier P. Bacterial contamination of multiple-dose vials: a prevalence study. *Am J Infect Control*. 2004;32(1):12-16.
9. Green KA, Mustachi B, Schoer K, Moro D, Blend R, McGeer A. Gadolinium-based MR contrast media: potential for growth of microbial contaminants when single vials are used for multiple patients. *AJR Am J Roentgenol*. 1995;165(3):669-671.
10. Dominik RH, Segebade IE, Taenzer V. Risk of microbial contamination of iodinated contrast media on multiple use of large-volume bottles. *Eur J Radiol*. 1995;19(3):198-205.
11. Paparella S. The risks associated with the use of multidose vials. *J Emerg Nurs*. 2006;32(5):428-430.
12. Chen KT, Chen CJ, Chang PY, Morse DL. A nosocomial outbreak of malaria associated with contaminated catheters and contrast medium of a computed tomographic scanner. *Infect Control Hosp Epidemiol*. 1999;20(1):22-25.
13. Moore ZS, Schaefer MK, Hoffmann KK, et al. Transmission of hepatitis C virus during myocardial perfusion imaging in an outpatient clinic. *Am J Cardiol*. 2011;108(1):126-132. doi:10.1016/j.amjcard.2011.03.010.
14. Pañella H, Rius C, Caylà JA, Barcelona Hepatitis C Nosocomial Research Working Group. Transmission of hepatitis C virus during computed tomography scanning with contrast. *Emerg Infect Dis*. 2008;14(2):333-336. doi:10.3201/eid1402.060763.
15. Patel PR, Larson AK, Castel AD, et al. Hepatitis C virus infections from a contaminated radiopharmaceutical used in myocardial perfusion studies. *JAMA*. 2006;296(16):2005-2011.
16. Sardan YC, Zarakolu P, Altun B, et al. A cluster of nosocomial *Klebsiella oxytoca* bloodstream infections in a university hospital. *Infect Control Hosp Epidemiol*. 2004;25(10):878-882.
17. Cona MM, Bauwens M, Zheng Y, et al. Study on the microbial safety of an infusion set for contrast-enhanced imaging. *Invest Radiol*. 2012;47(4):247-251. doi:10.1097/RLI.0b013e31823c0f87.
18. Gretzinger DT, Cafazzo JA, Ratner J, Conly JM, Easty AC. Validating the integrity of one-way check valves for the delivery of contrast solution to multiple patients. *J Clin Eng*. 1996;21(5):375-382.
19. Tress BM, Hellyar AG, Pennington J, et al. Multiple doses of contrast medium from a single container: bacteriological studies. *Australas Radiol*. 1994;38(2):115-118.
20. Blake MP, Halasz SJ. The effects of x-ray contrast media on bacterial growth. *Australas Radiol*. 1995;39(1):10-13.