Assessing Filling Technologies For Contamination Risk

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ABSTRACT

The authors compare four well-established aseptic filling technologies, open vial, ampul, blow-fill-seal (BFS) and prefilled syringes, to the recently developed closed-vial technology with regards to the exposure risk from viable particles from the air supply. Containers (e.g., vial, syringe barrel, or ampul), container closures (e.g., stoppers, or plungers), and filling needles have all been taken into account and weighted by exposed surface and exposure time. The study assumes that all of these technologies are normally operated under controlled environmental conditions in accordance with worldwide GMP standards and with appropriate attention to generally accepted sterility assurance guidelines, including use of an ISO 5 environment during the filling operation. The analysis showed that two technologies, BFS and closed vial technology, significantly reduce the risk of contamination due to exposure to the environment. The reduction factor for this risk can exceed 100 compared with open containers.

A recently published article in *Pharmaceutical Technology Europe* by Haag pointed out the risk of contamination due to exposure of the internal surfaces of the container during the filling process (1). The article described the concept of an environmental risk approach based on exposure to laminar airflow, which is susceptible to carrying viable particles. High efficiency particulate air (HEPA) filters are very effective at eliminating viable particles from ISO5 environment but the absence of particles can never be guaranteed. Haag's preliminary analysis was conducted with only three types of containers (e.g., large vial, small vial, and ampuls) and considered entry of the bacteria only through the container neck (1).

The scope of this analysis has been extended to include more packaging types used for aseptic filling of liquid products. In addition to vials and ampuls, prefilled syringes, blow-fill-seal (BFS) containers, and closed vial technology have been added. The sources of contamination have been systematically screened so other parts (e.g., stoppers, plungers, and filling needles) have been taken into account.

Closed vial technology has been used to fill stability batches of Synflorix (pneumococcal vaccine, GSK Biologicals) and granted approval by the European Medicines Agency (EMA). To illustrate the effects of minimizing exposure on the risk of contamination, media fill data in normal and challenging situations using closed vial technology have been generated and are presented in this article.

To avoid confusion between different techniques, lyophilized products have been kept outside of the scope of this article. Nevertheless, a similar approach is easily applicable.

This article focuses on risk due to environmental contamination during filling operations. Many other risks for the patient are present, such as contamination generated by human intervention (e.g., machine breakdown or component transfer), contamination due to cracks in glass containers, contamination due to

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inadequate sanitization of contact parts, or presence of glass particles when ampuls are opened. These sources of risk are not taken into account in this article.

METHODOLOGY

The applied methodology can be described by the following four steps. The outcomes of each step are summarized in Table I.

Definition of container types

Several containers are used for aseptic filling of injectable liquid products. The main ones are:

- The ampul, which is the original container and still by far the most frequently used primary packaging throughout the world.
- The open vial, which replaces the ampul in many regions such as Western Europe and North America. Two formats of vial necks are frequently used, the small neck vials like 2R and 4R and the large neck for 6R vials and bigger. Glass vials are widely used whereas polymer vial use is still limited.
- The prefilled syringe, which is often used for expensive biological drugs in North America. Again, glass syringes are used more frequently than polymer syringes. Cartridge technology has been assumed to provide very similar results compared with prefilled syringes and therefore was not specifically analyzed.
- BFS technology, which is widely used for both small- and large-volume parenteral infusions as well as noninjectable aseptic applications, such as ophthalmic, respiratory therapy, or nasal drugs.
- Crystal closed vial technology, which has been developed to address, among other things, the issue of contamination risk due to environment and operators. This vial is made of cyclo-olefin co-polymer (COC) and supplied clean, closed, and sterile. The vial is filled by a needle piercing the stopper; the trace of the needle is then re-sealed by a laser (2).

Definition of container format

To allow comparison between containers, the focus has been put on containers designed for a product volume of 2 mL, one of the most frequently used formats for injectables.

Identification of critical surfaces

Critical surfaces for potential contamination are detailed in Table I. The most obvious one is the container itself. The entry surface provides a good estimate to correlate with risk of contamination rather than the entire internal surface of the container.

Another main surface that may potentially be contaminated is the internal surface of container closure components, such as the vial stopper and syringe plunger. Before closing the container, these surfaces are fully exposed to the laminar airflow and are in contact with equipment parts, such as the vibrating bowl and ramps, that may transfer contaminants. Usually, these container closures are loaded in sorting bowls in large quantities. In such cases, the corresponding exposed surface can be estimated by the area of the bowl open surface ($\pi \times$ bowl radius^2) divided by the number of components inside the bowl and multiplied by the share of surface at risk (i.e., the internal surface of the closure).

The needle, or mandrel for BFS, is also a source of possible contamination when it is fully exposed to the ISO5 environment. A contaminant can stick to the needle surface, to a liquid drop, or close to the exit holes and be brought inside the next vial by the product flow. The needle surface at risk to be considered for the present study is the surface in contact with either the product or the container.

Quantification of the exposure time

The exposure time is a crucial factor because the longer the exposure time to the ISO5 environment without specific protection, the higher the probability of contamination.

As an example, the glass vial component is exposed during the cooling process after the depyrogenation tunnel, during the filling process, and until being stoppered. Any contamination occurring before or inside the depyrogenation tunnel will be destroyed and therefore be without effect. Any contamination occurring after proper stoppering will affect the external part of the vial and therefore not the prod-

Table I: Qualitative identification of container, format, source of product contamination, and exposure time.

Container type	Container format	Source of contamination	Exposure time	
			Starting	Ending
Open vial	2R glass	Vial	Depyrogenation tunnel, being cold enough	Stoppering
		Stopper	Loading in bowl through port	Stoppering
		Needle	End of previous vial filling	End of current vial filling
Prefilled syringe	2 mL glass	Syringe barrel	Tub opening	Plunger placement
		Plunger	Loading in bowl through port	Plunger placement
		Needle	End of previous syringe filling	End of current syringe filling
Ampul	2 mL glass open	Ampul	Depyrogenation tunnel, being cold enough	closing
		Needle	End of previous ampul filling	End of current ampul filling
Blow-fill-seal	2 mL polyethylene	Container	Parison cutoff	Beginning of filling
		Mandrel	End of previous container filling	Beginning of current container filling
Closed Vial	2 mL cyclo-olefin co-polymer	Stopper surface touched by the needle	Loading	Piercing
		Piercing hole	Piercing	Laser resealing
		Needle	End of previous vial filling	Beginning of current vial filling

uct inside the vial. To ease the use of the model, special events linked to improper container processing (e.g., equipment stops or break down, or manipulation by operators) have not been taken into account, but these events would of course lead to higher risk of contamination.

RESULTS

Quantification was performed according to the categories in Table I. The information used was obtained from several sources, including equipment users and Internet websites. All the listed operations were assumed to be performed under a unidirectional laminar air flow with a speed of 0.45 m/sec. Turbulences were not taken into account unless specified for some chapters. The quality of viable particle content of the laminar airflow is assumed to meet Class ISO5 requirement and has also been assumed to be identical for all five technologies.

Equipment can have a specific effect as well, because low speed equipment may signify increased exposure time. Therefore, a similar capacity of 150 units/min has been considered.

Open vial

As listed in Table I, three potential sources of contamination were identified: the open vial, the stopper, and the needle.

For the vial, contamination by airflow can occur through the vial neck. A 2R vial has a neck diameter of 13 mm, with a real opening of 7 mm diameter, according to the ISO standard (3). Only the opening is considered as a source of contamination entry. Contamination on the remaining surface is assumed not to enter the vial after stoppering and therefore does not alter the product quality.

The exposure time, from depyrogenation tunnel until stoppering, is estimated to be approximately 15–20 min based on user comments. A significant part of this time is used to cool down the vial before filling. Contamination occurring when the vial is still hot is not a major risk because bacteria can be killed by intrinsic vial heat. Therefore, the real time at risk was considered to be approximately 8 min.

The second source of possible contamination is the stopper. In the case of filling inside an isolation barrier, the stoppers are loaded either from a sterilization vessel or

from rapid transfer port (RTP) beta-bags. In both cases, once the port is opened, the stoppers are exposed to the filling environment. The stoppers are transferred to a vibrating bowl and then brought to the stoppering station through various ramps. A good estimate is that reloading of stoppers takes place every 30–40 min. This means that the average exposure time is a little more than 20 min as reload takes place before complete emptying of the bowl and the ramps.

Regarding the exposed surface, it is necessary to take into account that many stoppers are stacked on each other in a vibrating bowl and therefore not permanently exposed. The vibrating bowl comes in several sizes, but a 600 mm diameter is a good approximation for a line with a capacity of 150 vials/min. The presence of a loading buffer has not been taken into account. The presence in the ramp has been considered negligible compared with the time spent in the bowl and, moreover, stoppers usually present the external part to the airflow, hence a reduced risk. Only the part of the stopper introduced inside the vial presents a risk of contamination, and represents approximately 40% of the entire stopper surface. Therefore, the calculation of exposure is based on the air entering the vibrating bowl and the share of distribution between noncritical and critical stopper surfaces. If a bacterium sticks to the internal surface of the bowl, it is assumed that sooner or later it will transfer to a stopper.

The last component is the filling needle. The filling needle remains exposed during the entire filling process but, considering each vial independently, the exposure time is limited to a single filling time. The critical surface is limited to the area accessible to a drop, and is estimated to be 2 mm^2 for a standard needle. Another point to consider is that the critical surface is either parallel to the air flow or protected underneath the needle, so the risk of contamination is reduced because there is no perpendicular airflow. Therefore an angle of 30° has been taken into account as flow can be turbulent, especially under the needle holder.

Needle exposure time is limited, because pumps usually have a filling capacity of 2400 small vials per hour according to equipment manufacturers, or one fill every 1.5 s.

Prefilled syringes

The process for syringes is similar to that for vials. Three similar components are involved (i.e., barrel, plunger, and needle) and a parallel evaluation can be conducted. The main difference consists in a reduction of the exposure time for the syringes versus the vials as they are usually not processed through a depyrogenation tunnel but are supplied in ready-to-use tubs.

For the model based on a 2 mL syringe, the selected barrel has an internal diameter of 8.65 mm according to the ISO standard (4). Again, as for the open vial, the barrel opening is considered as a potential source of contamination entry.

With ready-to-use tub packaging, the exposure time for the syringe barrel is limited to the unwrapping process, the exit of syringes from tubs, the weighing time before and after filling for in-process control, the filling time, and the conveying time for all these steps until plunger placement. This time is limited and varies according to equipment complexity, buffer capacities, and speed. A total time of one minute has estimated to start the closing of the first syringe after unwrapping with no buffer assumed. As there are approximately 100 syringes per nest, this represents an average additional time of 20 s for each syringe.

The standard plunger has a front surface of 9.2 mm to ensure tightness in the 8.65 mm barrel. This surface is at risk as it will be directly in contact with the product. The rest of the surface (i.e., sides and back face) represents approximately 85% of the plunger surface. An average exposure time of 20 min, similar to open vial stopper, is a good approximation. The size of the vibrating bowl is smaller compared with that used for open vial stoppers so a diameter of 400 mm has been estimated.

The exposed surface and the exposure time for the filling needle are similar to the open vial model.

Ampuls

Table II: Quantification of exposure risks based on exposed surface, exposure time and a unidirectional airflow of 0.45 m/s.

Container type	Source of contamination	Surface (mm^2)	Exposure time (sec)	Air volume (m^3)
Open vial	Vial entry	38.5 mm^2	480	8.3×10^{-3}
	Stopper bowl surface per stopper × ratio of critical stopper surface	37.7 mm^2	1200	20.4×10^{-3}
	Needle tip x sin30°	1 mm^2	1.5	$<10^{-6}$
	Total			28.7×10^{-3}
Prefilled syringes	Syringe barrel entry	58.8 mm^2	80	2.1×10^{-3}
	Plunger bowl surface per plunger × ratio of critical plunger surface	6.3 mm^2	1200	3.4×10^{-3}
	Needle tip × sin30°	1 mm^2	1.5	$<10^{-6}$
	Total			5.5×10^{-3}
Ampul	Ampul entry	50.3 mm^2	360	8.1×10^{-3}
	Needle tip × sin30°	1 mm^2	1.5	$<10^{-6}$
	Total			8.1×10^{-3}
Blow-fill-seal	Air contained inside the vial			0.002×10^{-3}
	Mandrel/nozzle tip × sin30°	25.1 mm^2	10	0.113×10^{-3}
	Total			0.12×10^{-3}
Closed Vial	Stopper surface touched by the needle	3.1 mm^2	120	0.17×10^{-3}
	Needle tip × sin30°	47.1 mm^2	1.6	0.03×10^{-3}
	Total			0.20×10^{-3}

The ampul differs from the two previous containers by the absence of a part to be inserted, hence the elimination of this secondary source of potential contamination. The most classical ampul is the open type. For a content volume of 2 mL, the top opening of the ampul has a diameter of 8 mm according to ISO standards (5). This surface is considered as the entry path for contaminant even if a narrow surface of approximately 6 mm is present below.

The classical ampul is processed by washing and a depyrogenation tunnel as for vials. After this process, the ampul must be cooled. Thinner glass means the cooling is more rapid than for glass vials. A good estimate is that the cooling time is approximately 10–15 min, with 6 min without contamination risk because the glass is still hot enough to kill bacteria.

The exposed surface and the exposure time for the filling needle are similar to the open vial model.

Blow-fill-seal

The concept of BFS is to mold the container, fill it immediately, and seal it, all at the same location (6). This technology minimizes exposure as the container is immediately processed within the same cavity and within a short period of time.

Vials are formed in a mold with vacuum assist applied to the external surface of the container and, in the case of polypropylene resin, a brief blowing pressure applied with sterile air, along with venting. Therefore, for a container of 2 mL capacity, a good estimate is that a net 2 mL of sterile air has been briefly retained inside the container, before the filling step.

The equipment output is approximately one container per cavity every 12 s. During part of this time, approximately 10 s, the mandrel/nozzle is exposed to the controlled environment. The exposed surface is estimated to have a diameter of approximately 8 mm.

Closed vial technology

The filling process for closed vials consists of loading closed and sterile vials, piercing the stopper with a noncoring needle, delivering the liquid, and resealing the stopper with a laser (2).

The two exposed areas are the top of the

vial and the needle. The inside of the vial is never directly exposed to the environment. Contamination of the top of the vial could potentially lead to entry of a contaminant during piercing, the contaminant being carried by the needle inside the vial. Therefore, a surface estimated to be equal to the diameter of the needle is considered at risk.

Because indirect contamination by needle carry-over is not obvious, stoppers have been contaminated with 10 bacteria before piercing. That experiment has shown that carry over of contamination can occur, but does so in less than 20% of the cases. In comparison, the statistically calculated result in case of complete carry over would be 48%. Nevertheless, this risk reduction factor has not been taken into account in the calculation.

The exposure time is limited because there is no cleaning or sterilization of the vial before filling. Vials are supplied in boxes of 252 pieces, which are automatically loaded. A good estimate is that 60 vials are in the conveying system from loading table to filling station and that a new box is opened when half a box remains as buffer. According to this calculation, a vial would average 2 min of exposure before being filled. After filling, the stopper returns to position with the two lips of the piercing trace in tight contact. The contact is so tight that most vials can pass a dye test with −300 mbar challenge pressure and entry of a contaminant is considered to be highly improbable. Moreover, laser resealing after filling takes place within few seconds.

A second possible source of contamination could be entry of bacteria during filling through the grooves located on the needle wall. These grooves have been designed to allow exit of the air during filling of the liquid to prevent overpressure inside the vial. As there is a significant airflow moving out of the vial through the grooves, the risk of contaminant entry by these grooves is considered negligible.

The third source of potential contamination is the needle itself. The needle used to fill small volumes has a diameter of 2.0 mm. As the needle penetrates the vial, this penetrating surface is critical. The penetration depth is variable but 15 mm is standard and is used for the model. The cycle time is 2.4 s but the needle is protected inside the vial during approximately 0.8 s.

Potential effect of exposure

Aseptic filling is, as its name indicates, a process in which sterility is not guaranteed. Despite recent developments such as isolation technology, the risk can never be completely eliminated. Several sources of potential contamination can be identified in aseptic filling including the quality of air supply delivered to the filling line, operator presence, partial sanitization, contamination during transfer, and operator errors.

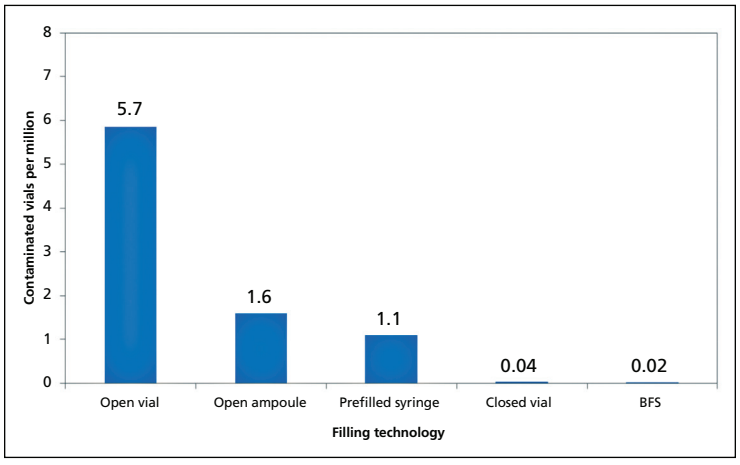
International GMP standards require aseptic filling to be performed in a Class ISO5 environment according to ISO 14644-1 where acceptable particle content is defined (7). European standards further refine the definition as they introduce the concept of viable particles (i.e., colony forming units or cfu). The Revision of Annex 1 of the Eudralex (8) has defined that the content per cubic meter of air should be less than one cfu. The concept of using settle plates is also present, with a limit of less than one cfu settled by 4 h on a 90 mm plate.

Very few monitoring data are publicly available but Vetter has communicated results obtained at the International Society of Pharmaceutical Engineering (ISPE) meeting in Tampa in 2006 (9). These results cover four years of activity from 2002 to 2005 on four syringe filling lines operated under a restricted access barrier system (RABS) in a Grade B clean room with the additional constraint that doors cannot be open during operations. During this period, they performed approximately 14,000 environment controls (e.g., air sampling, settle plates, and contact plates) and recorded 11 deviations, approximately 0.1% of all the environmental monitoring measurements.

Assuming such a deviation rate is representative of aseptic filling under a high quality barrier system, it can be realistically evaluated that there is one cfu every 5,000 m^3 of air. As a result, the risk of contamination in each type of container is illustrated in Figure 1.

Figure 1 shows that the risk of contami-

Figure 1: Number of contaminated vials per million vials filled assuming the presence of one colony forming unit per 5,000 m³ of air. BFS is blow-fill-seal.



nation for prefilled syringes is about one container per million. This value is in agreement with the media fill data communicated by Vetter during the same ISPE conference in Tampa (9). They reported to have filled, on the four equipment lines protected by RABS, one million media fill units with one case of contamination.

Reduction of exposure risk affects barrier requirements

As two technologies provide clearly different exposure risk compared with the others, barrier constraints to surround filling equipment for these containers have been challenged by the industry. BFS, being widely used for many years, has received particular attention from the authorities, and it is well accepted that the filling equipment can be surrounded by a Grade C clean room according to Annex 1 from the Eudralex (8). On the contrary, a Grade C environment for open vials and syringes imposes the use of isolators whereas RABS must be located in ISO7/Grade B environment according to the same source. The only restriction for BFS is that operator gowning should meet the requirements of a Grade B environment (8).

No definition has been set for closed vial technology, because it has been on the market only a short time. Nevertheless, the manufacturing of the first product submitted for approval has been based on the philosophy that the container provides additional protection compared with open containers.

Therefore, a new barrier has been defined, built, validated in ISO8 environment, and presented to the authorities. This barrier, called closed vial filling system (CVFS) containment, is defined as:

"An aseptic filling system providing an environment achieving uncompromised Class 100 / Grade A / ISO 5 protection that surrounds containers which are delivered closed and sterile inside, are filled through their stoppers and then immediately re-sealed to preclude the possibility of microbial ingress."

The CVFS is suitable for installation in an ISO8 or Grade C clean room as long as the following key characteristics, defined by a quality-by-design process, are respected:

- Only closed containers are processed inside the containment.
- The containment is made of a rigid wall enclosure that provides full physical separation of the aseptic processing operations from operators.
- HEPA-filtered unidirectional air flow is continuously supplied from the ceiling of the enclosure. The environmental control system operates primarily on the principle of aerodynamic separation (air overspill) as defined in ISO 14644-7. An open bottom with air exit inside the surrounding environment is appropriate for classical products. For highly potent or toxic products, a closed bottom is recommended to maintain operator protection. In the case of an open bottom, design prevents any accidental access of operator or turbulence to the critical area.
- Doors must stay permanently closed until the batch is completed and the line has been cleared of all finished goods. Doors are locked and interlocked with records of opening by alarms during operation. In the case of a door opening, all material still present inside the CVFS (e.g., empty vials, filled vials, bulk in fluid path, caps) must be considered as contaminated and must be discarded.
- Doors must be fully equipped with gaskets to prevent intrusion of contaminants.
- Glove ports are used to access all areas of the enclosure that must be reached by an operator during filling operations.

ALL FIGURES ARE COURTESY OF THE AUTHORS

Table III: Compilation of media fill data using closed vial technology. CVFS is closed vial filling system.

Site	Surrounding environment	Barrier system	# Media fill	# Media fill units	# Contaminated units
Aseptic Technologies	ISO8	CVFS	15	74538	0
Client site	ISO7	CVFS	3	14100	0

- Entry of materials, such as closed and sterile containers, sterile caps, sterile fluid paths, environmental monitoring materials, and tools, is performed via transfer systems that prevent exposure of sterile surfaces to operators and environments which are not Class 100/Grade A/ISO 5. Among potential solutions are:
  - o Entry through rapid transfer ports (RTP) using beta-bags for solid parts or SART connector for liquids
  - o Entry through vapor hydrogen peroxide (VHP) airlock
  - o Entry through an e-beam sterilization tunnel to ensure sterility of critical surfaces (e.g., stopper top surface).

The recommended cleaning procedure of a CVFS is a high-level disinfection of all non-product contact surfaces with an appropriate sporicidal agent before batch manufacturing. Performance of sanitization by VHP can also be foreseen but in the case of an open bottom, the VHP would address the entire filling room.

All product contact parts (i.e., needle, tubing) must be sterilized by either irradiation or autoclave. Entry of these parts must be conducted according to the above techniques for material entry to maintain an uncompromised sterility assurance level.

Media fill data using closed vial filling system

Closed vial technology has been recently developed and equipment availablity is limited, so media fill data sets are not as large as those from other technologies. Therefore, media fill data have been compiled from various sources as shown in Table III.

In addition to the data collected in pharmaceutical environments, challenging media-fill studies have been conducted, one in a workshop with the operator gowned as for ISO8 environment and one in an ISO8 clean room with the operators gowned as for ISO8 requirement but without a glove installed on the CVFS. The outcome of the first series of tests, with five media fill runs generating 26313 media fill units, is that no contaminated unit has been seen. The second test, performed on a much smaller quantity (523 vials) also found that no vials were contaminated despite the operator entering his arms with simple glove protection only inside the barrier to set up filling tubing and for other interventions..

Similar challenge studies have previously been conducted and the results published for BFS technology (10, 11).

CONCLUSION

Aseptic filling carries an element of risk by definition, primarily because of the introduction of the human element in the production environment. Recently, Vonberg and Gastmeier performed an in-depth analysis of an outbreak database. This database contains more than 2000 outbreaks recorded, with 261 of them related to nosocomial infections due to drug injection. The 128 most recent ones with publication of causes, representing 2,250 infected patients, have been analyzed in detail. Three quarters of them were linked to the drug and 20% of these drug products were badly manufactured. According to these data, it is estimated that 2% of patients affected by outbreaks leading to nosocomial infections were contaminated by badly manufactured injectable drugs (12). This number can be extrapolated to all nosocomial infections, 1.7 million patients in the US in 2002 (13), concluding that approximately 30,000 patients have been infected by badly manufactured injectables, of which 3,000 died.

To illustrate that the risk of aseptic filling is well recognized, the EMA considers a filling process to be acceptable if not more than one contaminated unit is detected within more than 10,000 media fill units. For example, getting one posi-

tive unit among 12,000 media fill units means a contamination rate below 0.04% with a 95% confidence limit.

Very advanced technologies such as BFS and closed vial technology are sources of improvement as they can reduce the risk of product contamination by the surrounding airflow by more than two logs compared with classical technologies such as open vial filling. The media fill data, obtained in both GMP and challenging conditions, show how a low exposure filling technology can prevent accidental intrusion of contaminant in an injectable drug.

It is reasonable to assume that several other potential contamination sources (e.g., operator mistakes, inadequate sanitization, or glove contamination) may result in similar differences as the probability of contamination is always proportional to the probability of entry.

According to data from Vonberg and Gastmeier, such improvement may represent several thousand of nosocomial infections avoided in the US each year (12).

Such large differences in contamination risk suggest that the pharmaceutical industry should think about innovative solutions to improve quality for patients. Regulatory authorities have endorsed such innovative solutions with acceptance of CVFS in ISO8 environment and with the statement that BFS equipment in ISO8 environment meets GMP standards. With the same philosophy, FDA is increasingly emphasizing concepts instead of terminology (14). In particular, FDA recommends designing manufacturing processes based on scientific evidence of robustness. The calculation conducted in this article shows that higher confidence could be placed in BFS and closed vial technology compared with other open container technologies.

Using the most advanced technologies and requiring more science-based design are probably the best ways to reduce risk for the patient. Moreover, the pharmaceutical industry will benefit from simpler and more robust filling technologies.

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