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A single-use isolator for aseptic filling, innovation or heresy

Abstract

GTP Nano is part of GTP Bioways, a Contract Development and Manufacturing Organization (CDMO) dedicated to innovative therapies. The company was created in 2018 with the aim of offering sterile drug nano-manufacturing and vial/syringe aseptic filling services for the innovative therapies sector (such as protein, cell or gene therapies). GTP Nano focuses on sterile drug product formulation and aseptic fill finish for third parties. Its 700-square-metre facilities didn't previously exist and had to be built from scratch in compliance with European and global drug manufacturing requirements.)

Keywords: disposable isolator, parenteral production for high potent product, innovative therapy production, sterile manufacturing using robots, robot sterile manufacture, robot parenteral manufacturing, sterile innovation, disposable sterile isolator

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Regulatory requirements and innovation

Some would have been satisfied with a standard production line meeting the prerequisites of sterile manufacturing in a simple, tried-and-tested way; fixed-isolator sterile drug production lines have been known and accepted for now over 30 years.

Thanks to manufacturer improvements, meeting aseptic requirements no longer relies on the addition of surface bio-decontamination systems in the form of additional equipment. An expert in vaporized hydrogen peroxide processing is often no longer needed for the qualification and validation of decontamination cycles in isolator environments, as each manufacturer has a proven solution that comes with its equipment and is fully integrated into the isolators. Regulatory requirements are no longer an obstacle to implementing these isolators, which are now seen as the future of aseptic filling as they help reach levels of sterility assurance that classic clean rooms don't.

How many labs try to validate a 3-log reduction of *G. stearothermophilus* in class A/B environments, where human presence is accepted near the critical zone? On the other hand, since the isolator prevents human presence near the risk area, it helps reach a more than 6-log reduction or even, for some sterility assurance fans in our industry, a 12-log reduction. There sometimes lies the paradox of our trade: having to validate extreme levels in non-hazardous environments. I'll leave you to chew over this observation – surely we should expect to validate 12 logs when there's human presence and 3 logs when there isn't?

To date, an isolator is therefore the best technical solution for aseptic product filling in a GMP environment with all the constraints it brings. I'll borrow an image from my former boss who set up the first French isolator filling line for cytotoxics: "isolators and class A/B environments are like tennis and ping-pong: in one, you're inside the playing field and in the other one you remain on the outside."

Even though the new Annex 1 of the GMP gives a prominent place to the use and management of this kind of equipment, it doesn't help highlight the advantages of this technology compared to other types of manufacturing, probably to maintain increasingly high levels of requirements against the risks of contamination.

There is therefore a need for innovative uses of these isolators that can respond to all regulatory requirements, which I'm very familiar with, having read all the following guidance and re-read that of the ASPEC:

- FDA 2004[1]: Sterile drug products produced by aseptic processing-current good manufacturing practices
- PIC/S PI014-3, 2007[2]: Isolators used for aseptic processing and sterility testing
- PDA TR 28[3]: Process simulation
- PDA TR34[4]: Design and validation of isolator systems for the manufacturing and testing of health care products.
- EU GMP Annex 1, 2008 version[5]
- ASPEC 2015: Isolators: qualification and maintenance
- ISO 13408-6, 2004[6]: Aseptic processing of health care products-Part 6 Isolator systems
- USP 35 <1208>: Sterility testing: validation of isolator systems

There's a range of possible avenues when it comes to implementing lasting solutions for the production of sterile and potentially CMR (Carcinogenic, Mutagenic, Reprotoxic) substances, in particular when manufacturing chemotherapies. The implementation of these ethical molecules is challenging, and it's necessary to adopt an adequate level of protection for our operators and for the patients and doctors who will come into contact with the finished product.

But when looking at the manufacturing of this type of products and at companies like GTP Nano or any CDMO that manufacture them now or in the future, the main problem is no longer the introduction of such isolators, but above all their capacity to handle multiple products within the same production environment.

[1]https://www.fda.gov/regulatory-information/search-fda-guidance-documents/sterile-drug-products-produced-aseptic-processing-current-good-manufacturing-practice
[2]https://www.gmp-compliance.org/guidelines/gmp-guideline/pic-s-isolators-used-for-aseptic-processing-and-sterility-testing-pi-014-3-sept-2007
[3]https://www.pda.org/bookstore/product-detail/4345-tr-28-sterile-bulk-pharmaceutical-chemicals
[4]https://www.pda.org/bookstore/product-detail/4348-tr-34-design-and-validation-of-isolator-systems
[5]https://health.ec.europa.eu/system/files/2016-11/2008_11_25_gmp-an1_en_0.pdf
[6]https://www.iso.org/fr/standard/39782.html

For this reason, when it comes to our system, the main priority is the potential for quick and secure cleaning. At one stage in my career, I had to design and implement a decontamination system in lieu of production isolators at a time when few or no labs had innovated in this area. At the time, when creating our infrastructure, we were able to think about the best solution to add to our work instruments to free ourselves from the constraints of this cleaning. Single-use equipment wasn't as widespread back then.

A lot of single-use equipment now exists to address this industry issue and eliminate these types of sources of contamination. But only the isolator remained fixed and multi-use, despite the fact that it would have been conceivable, with advances in plastics processing and the control of classified environments, to use this type of technology to make this piece of equipment single-use and reach a new milestone in the process of aseptic filling.

A single-use isolator: how does it work?

Class A isolators must be operated in a well-described and now perfectly established way. Single-use isolators for the pharmaceutical industry aren't by themselves a true innovation. There are several companies that sell this type of system for the contained implementation of hazardous molecules, so bringing in a single-use isolators isn't at this moment in time a technical prowess. But fitting it into a sterile drug filling line in order to produce high-quantity batches represents a real technical innovation. Indeed, it's important to know and master the isolator as well as all of the in and out transfer data in order to put together technical specifications that perfectly respond to the needs of sterile drug manufacturing, in particular the implementation of a laminar or unidirectional flow at the filling and stoppering stages. The isolator itself must be perfectly conceived in order to avoid systematic adaptations that would lead to a constant revalidation of its very operation.

It must operate in a simple and reproducible way to allow for quick implementation and disassembly, so as to get rid of the constraints listed above. It must allow for secure and controlled operation in order to be permitted for use in class A environments. Experience of an industrial environment and of confined aseptic filling constraints help us quickly identify the type of isolator that's key to consider for single usage.

Indeed, all isolators in a classic filling line:

- container and stoppering system sterilisation
- equipment loading
- pre-filling preparation/feeding
- filling/stoppering
- capping

don't carry the same risks of contamination by the product and don't all necessarily need to be handled in the same way.

Especially as GTP Nano aims to be competitive within the CDMO market and can't afford to replace its entire filling line with each fill. For this reason, the filling/stoppering isolator was the most important candidate for single usage. Because products are filled and stoppered in this isolator, it's of course where the risk of environment contamination is highest.

If, during the effective filling and stoppering phases, this isolator can be isolated from the rest of the line to contain the risk, we're obviously limiting contamination dispersion and can dispose of this isolator only. Finally, if the crimping system we use allows us to eliminate vial breakage during capping, we could avoid any risk of contamination at this station and envisage to not have a single-use isolator for capping.

Therefore, the choice of a candidate for single use naturally drifted towards the filling-stoppering isolator, and we chose to insert it into a line with 3 other fixed ones, in order to cater for its needs: it's an isolator that's essential and vital to the whole line.

This isolator (pictures 1,2,3) was to be potentially handled in order to allow for the insertion of containers, so we asked for a minimum of 2 isolator gloves. We also needed to meet 21st century aseptic filling and stoppering needs.

6-axis robots were therefore decided upon and became a key recommendation in order to reduce the risk of contamination of the filled units.

Several industry-renowned companies already supply filling lines where handling is taken care of by such robots, but they are systematically integrated into the critical filling environment and must therefore be class A robots. Our wish from the start was to move the robots out of the critical environment. There are several reasons for this:

- robot maintenance in the case of a failure or malfunction
- reducing manufacturing costs of the chosen robot, plus the possibility of implementing them in class D or C environments
- automating filling in order to control the filling and stoppering phases and limit the time when filled units stay open
- relying on recipes rather than format parts for the filling of any type of container
- SMED (Single Minute Exchange Design) system change

We therefore turned to an isolator fitted with connexion sleeves in order to carry out the robots' tasks. This meant implementing extremely reproducible, tight-clearance systems for attaching the robots' arms in order to allow for the assembly and disassembly of gripping filling and stoppering tools, ensure repeatability of filling and stoppering with minimum variability and to allow for the introduction of a filling needle into a 6.25 mm collar and the handling of 6 mm in diameter syringe stoppers.

We've designed technical specifications that allow us to deliver all the sizing and handling needs that meet this list of constraints.

Picture 1

Citation: Pavan F. A single-use isolator for aseptic filling, innovation or heresy. *Pharm Pharmacol Int J.* 2022;10(5):152–155. DOI: 10.15406/ppij.2022.10.00378

Picture 2

Picture 3

Use and constraints of a single-use isolator

Single-use isolator doesn't mean cheap isolator. It's altogether identical to a fixed filling isolator, but can only be used once. It must therefore meet all NF ISO 14644 standards and, to this effect, undergo the relevant test and qualifications.

It's also a manufacturing tool and as such, implies that the supplier must fully master the whole list of prerequisites needed to qualify as a sterile industry vendor.

We chose a French supplier to implement the ultimate solution, and we asked them to put in place a flexible system for aseptic filling through the use of two types of pumps, one for viscous liquids (positive displacement pump), the other for conventional liquids requiring single-use equipment.

Thus, the single-use system fits perfectly into a continuum of isolators, each with its own function.

It's not an open line but indeed a closed filling line that takes into account the constraints of continuous but sequential filling. This allows operators to manage the filling line with minimal manpower. They can focus solely on feeding the aseptic filling and stoppering tool and leave high-risk tasks to the perfectly automated system that can take care of the entire hazardous area.

The qualification of this type of system requires perfect knowledge of aseptic filling activities in order to model and simulate operations to validate the whole process and implement an MFT (Media Fill Test) strategy that satisfies the regulatory requirements while ensuring the introduction of this innovation and never-before-used tools.

It's difficult to know how our industry and our regulatory bodies will react to this technological prowess, especially since there's no equivalent in the field of big pharma. Innovation isn't found in the routine large-batch production of molecules in large global laboratories. Innovation finds itself in the capabilities we'll need to develop in the near future to serve patients with targeted therapies to treat increasingly finely diagnosed pathologies that call for treatments tailored to each individual.

To this effect, gone are the days of high cadences and production tools designed for a single product. Production units will need to cater for both cost-effectiveness in the production of small runs and the manufacturing of small batches to avoid lengthy storage of products that would lead to losses for pharmaceutical labs, as they wouldn't find patients to use products manufactured in too large quantities.

This isolator being single use doesn't affect the entire qualification and validation activities – even though it's used only once. In fact, that may be a question for the regulator. Filters, connection systems, isolator walls and design elements must follow the same constraints as those of a fixed isolator.

Long term operation of a single-use isolator

The isolator we've conceived together with our supplier, and which has undergone all possible validations, is a very robust tool. Tens of thousands of MFT vials have been filled in all possible conditions in order to qualify the system's operating safety and thus improve the design of this equipment. Post-irradiation system sterility can be safely guaranteed for several days. With the assurance of system sterility, the filling of sterile products can be approached in the most positive way. The filling system is also flexible and allows for the filling of all types of fluids, high viscous as well as low-viscous, thanks to the option described above of using different types of pumps. Flexible isolator technology is now mature and allows for a finished product that responds to the expectations of industrial sterile equipment users.

Conclusion

There are no longer any pharmaceutical labs opening to manufacture products for third parties. If you look at the market of sterile outsourcing, there's no creation of production plants. The market relies instead on the takeover and recuperation of pre-existing players. Indeed, if we leave aside GTP Nano and GTP Bioways, the only production unit that was recently created for the outsourcing of sterile drugs is now over 10 years old (launched by Alain Sainsot). It's way too big a challenge for investors, and innovation brought about by conventional actors isn't disruptive, because of a lack of cooperation between players in our industry. They no longer embrace sharing and putting equipment and technological innovations face to face with the regulatory paradoxes we must face these days. The single-use isolator presents a real technological advancement that has the merit of existing in an industry that only allows change through continuity. We must review our offer to make sure the authorities regard disruptive technological innovations as an opportunity and no longer as an automatically debatable solution. This is the only way we'll remain a change industry and be able to relocate our resources and our drugs in a market where most of our products come from abroad and from countries that don't apply the same criteria we do.

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None.

Conflicts of interest

Author declares that there is no conflict of interest.

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