Vaccines Production. Challenges and trends in vaccine manufacturing

A journey through vaccines' history, highlighting steps and equipment involved in their complex aseptic production process

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WHITE PAPER

ABSTRACT

Vaccines manufacturing involve a complex aseptic production process that has been challenged in the current pandemic times. Vaccines' history and their evolution, points to consider when designing a vaccine manufacturing plant, technologies and main equipment used and the whole process qualification, are developed by authors showing the main aspects relevant to achieve a complete aseptic production assuring safety, integrity and efficiency of the process & product.

Introduction

Vaccines are a very effective method to prevent diseases and fewer scientific advances have helped save so many millions of human lives throughout history.

Edward Jenner, a family doctor from Gloucestershire, had observed that milkmaids working in the countryside were never contracting the feared disease smallpox as they had all contracted the much milder cowpox. In May 1796, he deliberately infected an eight-year-old boy with pus from a cowpox blister. He contracted cowpox but when his fever subsided, Jenner attempted to inoculate him smallpox and the boy did not contract it. Vaccination was born.

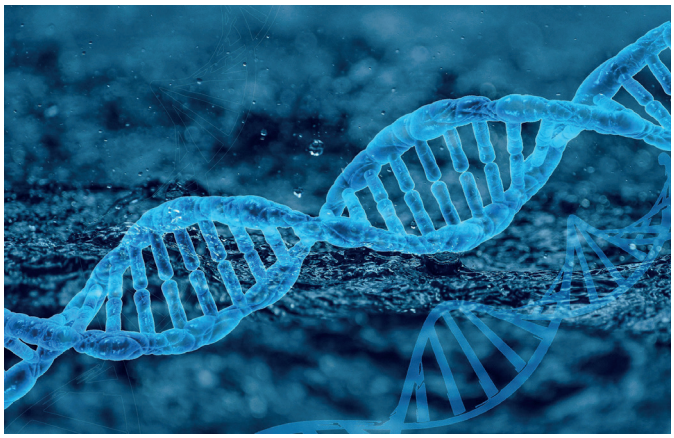
It is not easy developing a vaccine: According to WHO, only 26 diseases have a vaccine. Bringing a vaccine from laboratory to its use requires an average of more than 10 years (HIV vaccine has been under development for more than 35 years) and enormous investment.

During the 2020 pandemic, less than one year from the Wuhan SARS-CoV-2 identification; 301 vaccine candidates have been developed with 21 tested in humans and several of them already in the market helping to successfully fight the virus.

The way vaccine works is through immune system invader recognition, developing antibodies (blocking antigens) and T-lymphocytes (cell immunity memory).

To achieve this immunity, there are several strategies to obtain these vaccines:

- Using live attenuated germs mainly from the animal germ causing an illness like the human one (e.g. caused by bacteria, tuberculosis, typhus,... and caused by virus, measles, rubella, mumps, chickenpox,...) or a mix of several virus strains in reassortant vaccines (e.g influenza).
- Using dead or inactivated germs (e.g. . polio, rabies,...).
- Using parts of the germs (e.g. meningitis) or their inactivated toxins (e.g. diphtheria, tetanus,..).
- Using genetic vaccines utilizing recently developed technologies with DNA (e.g. SARS-CoV-2 spike protein in vector, AstraZeneca & Janssen) or mRNA (e.g. SARS-CoV-2 spike protein, Moderna & Pfizer-BioNTech).



Vaccine production capacity worldwide has dramatically increased with the pandemic, from 3,5-5,5 billion doses pre-COVID-19 to an estimated 14 billion by the end of 2021.

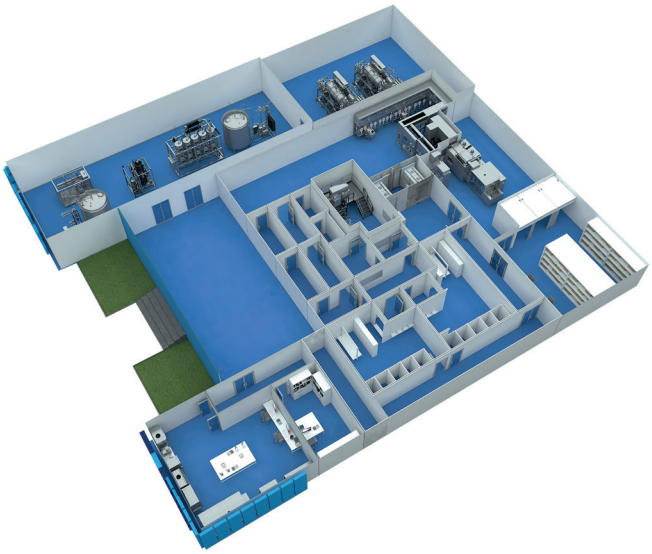
Due to the already seen difficulty with vaccines development, the strategy used until now has been to provide the bulk product to a reliable partner (CMO – Contract Manufacturing Organization) to complete the manufacturing process by performing the fill and finish operation. In recent times, even bulk production has been transferred to some partners to increase production capacity.

Once the clinical stage has been overcome successfully, a GMP industrial manufacturing process starts, with the associated difficulties: It is not enough having a formula; the needed know-how requires an appropriate transfer plan.

Such a challenging project requires a deep knowledge of the involved technologies and the capacity to design, specify and select the right equipment and facility, always having in mind that the process should be the starting point of any design.

The process, the first step to consider in the design towards ensuring aseptic conditions and the right quality product

When designing a new facility, the process that will take place should always be the centre in any critical installation design. It will not be the same design for a facility for a solid form as the design for a vaccine: essential rooms, utilities, HVAC, and additional equipment cannot be compared with each other.



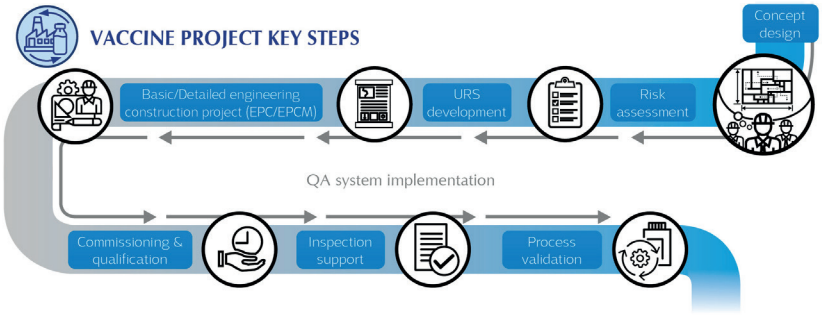
That is why from the initial idea to the final design a Conceptual Design shall be developed: The process to take place and its steps will be well defined and any regulatory and process needs shall be covered, addressing the main complexities linked to every specific pharmaceutical form.

Regarding regulations, in the case of vaccines, EU GMP Annex 1 on Manufacture of Sterile Medicinal Products and EU GMP Annex 2 on Manufacture of Biological active substances and Medicinal Products for Human Use are applicable. Also, FDA standards for Aseptic Production and Biological products shall be considered in the design.

As both people from the product and the product from the environment shall be equally protected, the challenge is defining the right conditions to protect the products quality and people/ environment. Usually, a dedicated facility for vaccines is the selected option, as it enables cross contamination prevention and protection considerations to be implemented much easier to control. Another point to consider is linked to the flexibility needed in the production according to the manufacturing processes taking place, that will influence the technology used and therefore the final design.

Once the technology aspects have been considered, regulatory requirements related to the type of equipment, room classifications and overpressures, as well as utilities (water for injection, nitrogen, compressed air) and process specifics shall be considered: compounding steps if starting from bulk, cold temperature conditions along the process, product transfer, raw materials addition, primary packaging materials handling, equipment involved, ...

And being a vaccine, effluents and waste management and staff protection are also key points to be considered.



Technologies designed to optimize an efficient and safe production

Just as vaccine production requires dedicated cleanroom areas for their manufacturing facility, high-quality pharmaceutical equipment plays a vital role in overall product quality and compliance with EU/FDA regulations. The evolution of technologies offers a value key in the development of integrated process equipment operating within an efficient critical process installation. An overview of main technologies that intervene in vaccines production process, focused on the fill and finish steps, provides knowledge on all stages of vaccine development and manufacturing and their requirements to provide a safe vaccine without any risk of contamination or contaminating.

Barrier systems

A vital component in the sterile production of vaccines is the barrier system enclosure, where the main objective is to provide a microbiologically controlled environment within which aseptic operations can be carried out and be protected from external contamination. This may be in the form of an Isolator where a grade C or D background is present or a cRAB's / oRAB's if the background is grade B. In all cases the barrier system enclosure will need to maintain an internal grade A (ISO 5) aseptic environment and operate at a positive pressure relative to the surrounding room.

Barrier systems are the preferred option according to regulations as they give full protection to product, people and the environment and they should be the selected technology unless the process does not permit the use of these systems.

In general, for production processes the grade A environment is achieved via HEPA filtered unidirectional laminar airflow over the complete area at 0.45m/s ±20%. This creates a uniform low velocity condition which is less likely to cause turbulence and in turn venturi effects that could have an adverse impact on the production operation. In most cases approx. 70-80% of the airflow would be recirculated and the remainder bled off, allowing 30-20% of fresh make-up air to be introduced. This make-up air can be pre-conditioned which when mixed with the recirculated air enables specific temperature and humidity parameters to be met in the working area.

Isolators differ from cRAB's and oRAB's, in that they are designed and tested to a level of leak tightness, ideally in accordance with a recognised international standard such as ISO 10648 or ISO 14644, which then enables them to be subjected to a sporicidal process, independent of the cleanroom itself. The introduction of a sporicidal process, for example vapourised hydrogen peroxide, significantly reduces the risk of microbiological contamination such as bacterial, fungal, yeast and mould spores, by employing a repeatable bio-decontamination cycle that is validated to achieve a Log6 reduction in biological indicator organisms.

Throughout the line active and passive viable / non-viable monitoring points would provide assurance of the grade A and microbial free environment.

Isolator systems, being of leak tight design, enables them to be used with aseptic products that are also toxic in nature. Typically exhaust filters in BIBO housings would be incorporated in the return air route. In addition, in such cases it is common for the Isolator to be equipped with suitable washing or misting systems, for operator protection and to avoid downstream cross contamination.

The barrier system would need to be sufficiently customizable to integrate with different filling lines, in particular Isolators and cRAB's where a sealed connection would be required with the filling machine bedplate. To enable continuous operation of the filling line there would be series of open, passive and active mouseholes where airflow losses and pressure cascades can be controlled.

Operator interface would be via a local HMI for control and monitoring of the system, however physical interface would be provided via multiple gloveports mounted in glass access panels located all around the barrier system. Increasingly though we are seeing a move towards robotic technology and gloveless systems as the need for operator interaction reduces, which would enhance the aseptic environment.

Clean air

At lab scale where flexibility is needed for new processes and barrier systems cannot be used, clean air technology is nearly always the best option.

The requirement for Grade A HEPA filtered air applies throughout the production process and extends to QA and R&D. Here primary containment barriers such as biological safety cabinets (BSCs) are recommended to ensure appropriate levels of protection for the staff, the product, and the environment.

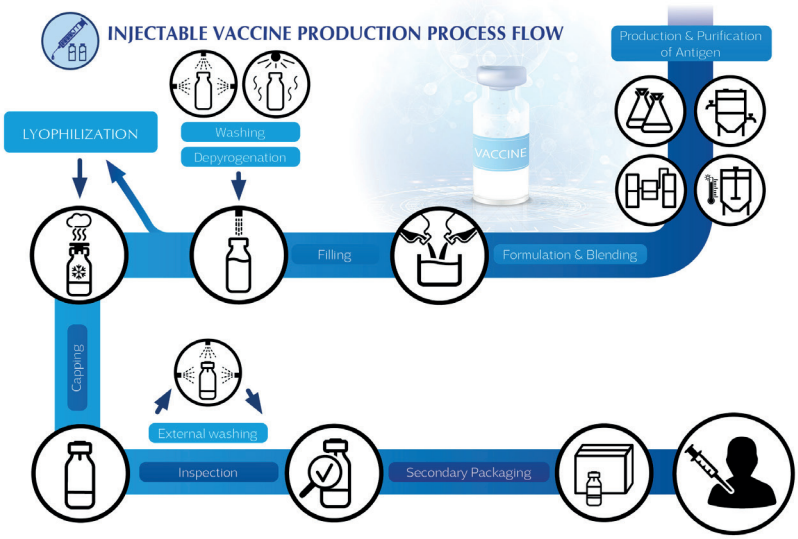
The most used BSCs are classified as Class II A2 by the European Standard EN12469 and the NSF49 American Standard and are suitable for GMP facilities, ensuring pharmaceutical products are produced consistently and controlled in accordance with the appropriate quality standards.

In a Class II BSC air is drawn into the work chamber through a front aperture creating a protective air barrier for the operator. Air travels under the worktop and reaches the plenum, where 70% is recirculated through the main HEPA filter to provide a laminar down flow of air on the work area and 30% is returned to the environment through a second HEPA filter. The working principle of a BSC provides operator protection by means of air inflow, product protection by means of laminar air down flow and environmental protection by means of the filtered exhaust air.

Optimal BSCs will be certified to a known standard by a third party and manufactured according to stringent quality standards. Above all due to the sensitive nature of the installation BSCs should facilitate carrying out efficient and effective cleaning and sanitising protocols, allowing operators safe and easy access to the work area. In this regard BSCs should be fitted with UV lamps, allow for VHP decontamination cycles, and include antimicrobial coating in the work area. This feature will prolong the effects of the cleaning processes already in place and greatly reduce the risks of contamination from one shift to the next. Other features should include an ergonomic design to reduce operator fatigue, intuitive HMI, safety alarms and fast and efficient access to the technical area to facilitate maintenance and reduce equipment down time.

It is worth remembering that any BSC is only as safe as the individual operating it. Operation, maintenance, and validation protocols/schedules should be adhered to as prescribed by the cabinet's manufacturer.

As for many other manufacturing plants that require strict biosafety rules, human presence is often identified as the greatest potential contamination source. Removing human presence in contamination sensitive environments is a trend that will see the introduction of robotic aids increase also for handling vaccine samples in QA and R&D inside microbiological safety cabinets and isolators.



Compounding

This chapter is focused on vaccines' fill and finish which means that the initial part before filling is not reviewed. Nevertheless, even if the vaccine bulk comes from another plant, there may be an initial step of dilution or addition of other components that should be taken into consideration.

Equipment is similar to the one used in any aseptic production process, with reactors and holding tanks that can undergo a steam-in-place process, of different size depending on the one of the batches, with auxiliary equipment such as autoclaves, filters and so on.

Filling

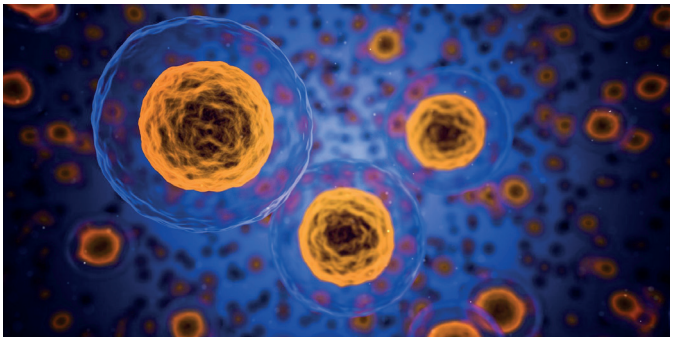
The filling process is one of the most important and risky operations for vaccines' production being the point where product is exposed.

Talking about vaccines means talking about large amounts of vials and high speed complete automatic fill and finish lines up to 600 vpm including vial washing machines, depyrogenation and sterilization tunnels, filling lines, capping machines, and sometimes external vial washers, integrated with some sort of barrier system to protect product, operators and environment, and the related environmental monitoring, data acquisition and control instrumentation.

It will always be an aseptic production process with all the related considerations and the filling machine shall be suitable for the type of packaging material, mainly vials and in a minor grade prefilled syringes for the low interaction of glass with the vaccines' components.

This part may deserve a whole article and it is not going to be discussed in this article, but it is worth mentioning that the integration of the filling machine with the isolator or RABS and with the whole line (vial washing, depyrogenation tunnel, freeze-dryer, capping machine....) is of great relevance to achieve a safe process.

The whole filling line should be appropriately designed and maintained, highlighting cleaning process and sterilization of its components as the 2 most relevant steps. Qualification and validation of the line are a must and should include the aseptic process simulation (media fill) as the last step before starting production.



Freeze-drying

There are plenty of human and animal health vaccines, although not all of them are freeze dried, (lyophilized). The main reasons to go to a lyophilization process are sterile manufacturing for parenteral application, better stability and dose potency, and improvement of shelf life, storage and distribution conditions.

In order to prevent direct contact with operators to avoid product contamination, freeze dryers are normally supplied with automatic loading/unloading systems and, as per the filling line, they are integrated with some sort of barrier system to protect product, operators and the environment.

Very often vaccine freeze dryer loading shelf area is 30, 40 or even 50 sqm with loading speeds of 400 vpm or higher and even higher unloading speeds and short turnaround time to prepare the units for a new batch as soon as possible. There are solutions to unload freeze-dryers very quickly in multi-lines to a buffer area to enable capping at a later stage using several capping units. Frequently chambers are pass-through type (loading from one side and unloading from the other).

The freeze-dryer automatic loading/unloading system must match the filling line speed even it is not a continuous process, it shall guarantee that filler and capper are not going to stop. Typically row by row systems are used: push-in/push-out, push-in/pull-out or with devices that can push or pull the rows of vials as requested. There are also shelf by shelf systems consisting of a vehicle that transfers the complete set of vials of one shelf at once, they require a previous row by row system to load the vehicle though. One or the other system is more adequate depending on the freeze-dryer configuration, number of freeze-dryers, size and requested loading/unloading speeds.

Half stoppered vials coming from the filler are transferred onto the freeze-dryer shelves, stoppered inside the freeze-drying chamber at the end of the lyophilization cycle and then closed vials are unloaded to go to the capper.

As a critical equipment in the manufacturing of aseptic biological injectable products, freeze dryers require inlet sterilizing filters to guarantee the integrity of the system, cleaning and bio-decontamination facilities: CIP with at least final stage with WFI and steam sterilization. There also needs to be facilities to treat contaminated

effluents and devices to prevent environment contamination as bag-in/bag-out exhaust filters.

Sterilization

Even though we are not discussing terminally sterilized products, in aseptic processing, all components must be previously sterilized and therefore sterilization process remains important. The most common methods are:

- Depyrogenation tunnel: It is the most common way to depyrogenate a large quantity of primary glass containers. In some old facilities and with small production batches a depyrogenation oven may be used. The tunnel is a pass-through system, usually connected upstream to the primary containers washing machine and downstream to the filling line where the primary containers are depyrogenized by HEPA filtered hot air while moving by means of a conveyor through the tunnel. It is a very safe system since there is no manipulation of containers.

- Autoclave: It is used to steam sterilize all those parts and components which will be in contact with the product and or the containers during the aseptic manufacturing process, such as rubber stoppers and components like hoses, filters, hoppers, filling needles etc. These elements are sterilized by means of saturated steam then transferred aseptically to the filling line. Regarding rubber stoppers, they are available as: Ready to use (washed and sterilized), Ready to sterilize (washed) or in bulk. The *Ready to use* do not require any sterilization of the stoppers but it is necessary to decontaminate the outer bag to ensure safe entry into the classified area. This is usually achieved by means of a pass-box provided with a hydrogen peroxide decontamination system. The ready to sterilize are usually available Tyvek bags and therefore sterilized in a pass-through saturated steam autoclave. In both cases the stoppers are protected and not manipulated after being sterilized. Stoppers in bulk are less expensive but require a more complex process and equipment to wash, sterilize and aseptically collect them to be transferred to the filling line.

- Outside sterilization: In some cases, due to the nature of the material (mainly resistance to temperature) or sterilizers availability, sterilization is done outside of the factory by a third-party company. In this latter case, independently of the sterilization method adopted (dry heat, moist heat, ethylene oxide, gamma-radiation.....) the sterilized material is contained in bags and therefore to safely enter into the aseptic area, the material needs to go through a pass box provided with a hydrogen peroxide decontamination system as per the stoppers ready to use.

Cold storage

Storing vaccines in cold conditions is essential to prevent them from losing their effectiveness or even becoming dangerous to patients; for this reason, high-quality refrigerators and freezers are an essential part of the supply chain. One key aspect of having cold storage in place for vaccines is that it can be adapted to meet long-term storage needs: in the case of COVID-19, once the pandemic comes to an end, manufacturers which have been developing and producing vaccines will be able to place any excess products into long-term cold storage. This means that they are ready to be distributed if the need arises again, rather than needing to establish new lines of production any time there is a new pandemic or epidemic of an existing isease.

Currently, the labels for mRNA technology based COVID-19 vaccines, state that the vaccine must be stored in Ultra Low Temperature freezers (ULTs) at temperatures between -80ºC and -60ºC. It can remain stored at these temperatures for up to 6 months. ULTs are therefore a vital part of the supply chain management for these sensitive and precious products.

Most ULTs use the same condensers and standard equipment found in home fridges; except they contain two refrigeration systems linked together to achieve these ultra-low temperatures. Because of their sensitive contents, ULTs are built with doors that lock, and a screen that always displays the inside temperature, which can range between -70 and -80 Centigrade.

It is important that ULTs use environmentally friendly gases such as ethane and propane, with a low Global Warming Potential (GWP) to reduce emissions and comply with upcoming stringent regulations. The footprint of these products should also be considered as they take up a lot of precious space. The use of Vacuum Insulation Panels (VIP) will guarantee a greatly improved insulation rate compared to traditional polyurethane foam (PU) reducing the overall dimensions of the ULTs. Lastly a reliable temperature monitoring system should always be considered when string precious material in ULTs. The equipment should be connected to a centralised data collection system that will alert staff in case of malfunction and most of all of temperature rises. A backup system, fuelled by CO2 or LN2, can and should be installed on every ULT to prevent loss of product and to allow the implementation of a disaster recovery plan. As it may become necessary to vaccinate or re-vaccinate people once or even twice a year in the future, by implementing ultra-low temperature freezer storage, manufacturers will be able to keep on producing at the pace that works for them for one or two or three years building up sizeable reserves of the vaccine.

The limitations of standard ULTs, which have a maximum usable volume of 1000 litres, could push the request for large-scale ultra-low temperature freezers that can hold substantially more products. These walk-in storage facilities offer the advantage of storing large quantities of product (up to a few tons) in much less space with lower running costs.

Qualification & Validation process. Ensuring quality and integrity

In the pharmaceutical industry, the design developed for the process and facility, and selection of equipment & utilities are important: in fact, a poor design or wrong selection will adversely affect compliance with GMP.

But assuring the right quality requires providing documentary evidence of its correct performance: qualification and validation. From commissioning passing through qualification and ending with validation of all elements and the process itself: All steps and elements shall be tested to comply with FDA and EU cGMP standards.

Validation life cycle steps shall be followed: Starting with a VMP (Validation Master Plan) development, where the project details are explained as well as the validation strategy, continuing with a RA (Risk Assessment) where the non-GMP and GMP elements are discriminated and the split into critical and non-critical aspects made, to end up with the C&Q (commissioning and qualification)

of facility, utilities and equipment and the process validation in order to assure robustness and repeatability.

We must not forget that everything shall be handled under a quality assurance system that specifies how to produce documents, execute testing, and address any non-conformity or change.

This way applies to all pharmaceuticals and obviously to vaccines, too. So, what could be specific for vaccines?

Apart from the general GMP aspects, common to any pharmaceutical form, vaccines are nearly always injectables and they must then be sterile. As the active cannot stand final sterilization, they are produced by aseptic processing. Like all the aseptically produced medicines, this operation shall be tested by performing initial and periodic aseptic process simulations (media fills), one of the most challenging operations that can be performed in qualifications.

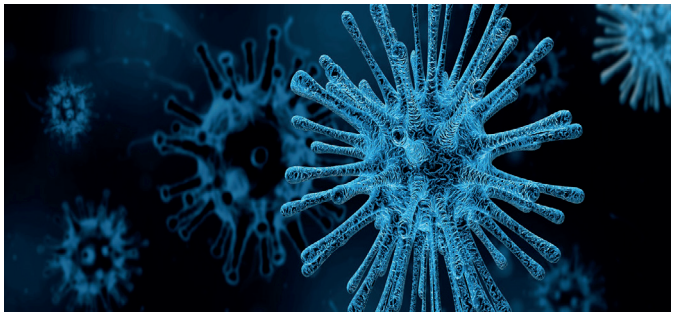
The other differential aspect of a vaccine is its need to be contained to prevent any contamination risk to the staff and environment. Testing HVAC systems, with the correct pressure cascade, including filters and ducts integrity and eventually isolators leakage, if used, becomes critical.

Another differential aspect of vaccines is their stability, usually very low. So, the conditions to store them, with very low temperatures, and even to produce them at low temperatures, must guarantee the cold chain, which is not always easy to confirm. So apart from the vaccine stability at ICH condition that must be proved during the required period, stability at refrigerator or room temperature shall also be checked.

The goal of all this qualification that has been explained is being sure that vaccines are produced under the correct standards and are always kept in the correct condition to guarantee its efficacy, preventing at the same time any contamination risk.

Conclusions

The impact of the COVID-19 pandemic worldwide has pushed not only pharmaceutical companies but also research centres and laboratories, together with the support of governments and public entities, to be actively involved in one of the greatest challenges in recent history. The phenomenon, which has led to increase knowledge on virus's nature, has also dealt with innovative manufacturing processes to develop the appropriate vaccines in the shortest period ever experienced. It is in this context that a growth awareness and interest on vaccines development and their manufacturing processes has been experienced not only from companies, but also from society as a whole



As a conclusion, some points from this article shall be highlighted on vaccines' production. Firstly, it is proven that vaccines are one of the key discoveries in the contribution to increase human being life expectancy. From the eighteenth century, until the twenty-first century vaccine production process technology evolution has simplified their production even the number of diseases with a vaccine is still very limited.

Vaccine production requires a protected environment, both, for the vaccine that is nearly always injectable, and for the environment, as it may be dangerous handling certain vaccines. Isolators and RABS are the option at industrial scale, while safety cabinets are the choice at laboratory scale.

In turn, vaccines' production lines are high speed glass lines (mostly of vials) and the resulting vaccines shall be kept at cold temperatures, 2 – 8ºC and sometimes, like with last generation mRNA vaccines, at ultralow temperatures (-80ºC) due to their poor stability. A freeze-drying process may provide the needed stability to the product simplifying its distribution and conservation.

Another relevant point is that being aseptically produced injectable products, process validation and aseptic process simulation are of paramount importance to assure a reliable quality on the resulting vaccines.

Complete integrated systems have proven to offer high output in all the phases of the injectable vaccine production. Involved in each stage of the complete manufacturing process, innovative integrated solutions including isolation

technology, sterilization and lyophilization applications, among others, are designed to ensure an aseptic and efficient production of pharmaceutical processes. Together with guidance in GMP Consultancy for regulatory compliance and GMP Digitalization & IT solutions for regulated processes & logistics management.

In spite of the challenges to produce a vaccine, the pharmaceutical industry has responded as one to the current pandemic, with several effective options that will hopefully soon lead the world to overcome the COVID-19 threat.

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About Telstar

Telstar, part of the azbil Group, is a company specialized in the development of engineering & construction projects, integrated process equipment and GMP consultancy solutions, including turnkey projects and critical installations, for companies associated with Life & Health Sciences (pharmaceutical & biotechnology, healthcare, cosmetic, veterinary and food & beverage industries, hospitals, laboratories & research centers). Acknowledged as one of the 10 major suppliers for the pharmaceutical industry, Telstar is one of the few international manufacturers able to offer integrated process solutions for the biopharmaceutical industry with in-house sterilization, freeze drying, containment, process water & waste treatment, clean air and cold storage technologies.