Scalable production of covid-19 injectable vaccines

Still a Transparency Blackbox

JENIK RADON
Advisor

DHWANI BABLA, GERARDO CANTO, DANIEL CHAN, REBECCA DIEFENBACH, DIMITRIOS FTHENAKIS, YUSHAN LOU, SHANNON MCKENNA, CERI-LUNE RENNEBOOG, & YUEXIN ZHAO
Team Members

Columbia University
in the City of New York

Summary

Since the global pandemic outbreak in February 2020, the vaccine manufacturing process has been at the forefront of conversations between public health officials, policy makers, industry experts and the public. Although much attention has been paid to the development and distribution of a COVID-19 vaccine, the fill and finish manufacturing process is also a crucial step to consider. Fill and finish manufacturing is currently fraught with proprietary knowledge, the details of which are usually only known by the manufacturer. This makes any sort of public planning extremely difficult as policy makers cannot accurately estimate the existing manufacturing capacity within the industry. This process also differs regionally; a fill and finish line in the United States may look different from a line in Europe, India or China. Additionally, availability of specialized equipment and materials is also highly regional and adds another layer of complexity to a global vaccine supply chain issue. Furthermore, the regulations and legal requirements to produce a vaccine vary substantially based on the country. In the United States the FDA requires very strict timeline and safety measures before a vaccine is authorized to be administered on human subjects, whereas other countries like Canada, The United Kingdom and the European Union have similar standards but an entirely separate regulatory and approval procedure. These factors coupled with the politicized nature of COVID-19 response and reporting has left the public with more questions than answers. This report aims to clarify these points and illuminate the complexity of the fill and finish manufacturing process in vaccine development.

Acknowledgements

This project may not have started had it not been for the director of The Millenium Institute of Immunology and Immunotherapy (IMII), Alexis Kalergis', desire to understand what it would take to create a domestic vaccine manufacturing center in Chile. IMII's dedication to scientific research and development in Chile is admirable and served as a constant reminder of how important our research was to the larger scientific community and the public.

We are thankful for the many industry experts who gave their time to our team in an effort to help us better understand the vaccine manufacturing process. We would not have been able to produce this report without your assistance.

Holly Battaglia, Lisa DeOerio and Steven Stoddard from Emergent BioSolutions (EBSI) for their expertise and technical knowledge in the fields of the fill and finish manufacturing process, project engineering management and epidemiology. Your hours of assistance helped us not only understand the fill and finish manufacturing process, but the challenges associated with vaccine development in general - particularly scalability and realistic timelines. Thank you for answering all of our questions, no matter how simple or abstract they were.

Dr. Felipe Tapia from the Max Planck Institute for his hours of research into the fill and finish manufacturing process and insights into the scalability of vaccine development, particularly in Europe. Thank you for taking the time to assist in an area outside of your field of expertise.

Andrea Taylor from Innovations in Healthcare and the Global Health Innovation Center at Duke University for sharing with us your research into current manufacturing commitments, available manufacturing capacity, manufacturing location and equitable distribution.

Mr. Sai Prasad from Bharat Biotech International Limited and Taslimarif Saiyed from CCAMP for engaging and sharing their work and knowledge on the vaccine manufacturing process in India and in their companies.

Finally, we'd like to thank the summer associates who spent months combing through technical documents and beginning to untangle the web of the vaccine production process. Their research and knowledge served as the baseline for our report: Colleen Elizabeth Neely - Columbia/SIPA Candidate 2021, Karla Sarai Rodriguez Glez - Monterrey Tech 2016, Laura Cobey Derrendinger - Columbia/SIPA 2004, Mira Isabel Baum - Columbia College 2020, Grace Pan - Columbia/SIPA Cand 2021, Rocio Pena Nahle - Columbia MS 2020, Nathalia dos Santos - Columbia/SIPA 2020, and Pedro Henrique de Barros Gagliardi - Columbia/SIPA 2020.

Table of Contents

I. Introduction

The COVID-19 pandemic is an issue that dominated the world's attention in 2020. Researchers, scientists, policy makers, advocates and the public are still struggling to understand the disease and how to control it without the introduction of a vaccine. Operation Warp Speed turned the vaccine development process on its head and brought this little-understood industry into the public eye. Moderna and Pfizer gained approval in Canada and the United Kingdom to inoculate their respective citizens and then gained emergency approval from the FDA to inoculate essential workers and eventually a broader population in the United States. As the first people receive their vaccines, there are still so many questions about the distribution and production of the vaccine. Up to this point, the public demanded an accelerated timeline to receive a vaccine, but this news helped to educate the public on the expected realistic timeline for the development of a vaccine. As early as April 2020, our team knew that the cognitive dissonance surrounding realistic timelines for the entire vaccine development process would be an issue. Although the news about a pending approved vaccine is promising, there are still many steps that the public needs to be aware of. Much attention has rightly been paid to the development of the COVID-19 vaccine and then the eventual distribution of a vaccine, but the steps in the middle of the supply chain are arguably some of the most important and misunderstood; human expertise and specialized manufacturers are critical to this step in the supply chain, in particular the fill and finish manufacturing process.

The fill and finish manufacturing process are one that is fraught with proprietary knowledge, the details of which are usually only known by the manufacturer; in short, this information is not available to the public. In fact, this knowledge has been referred to as a "black box" and has been depicted as such in technical manuals used in the vaccine industry. Because information on this part of the supply chain is proprietary, the public does not understand how specialized this industry is and the amount of time, resources, equipment and human capital that are required just to operate a fill and finish line. Special considerations must be taken for a sanitized area and oftentimes different types of vaccines cannot be produced in the same facility or on the same line. As an example, a technician on the fill and finish line must be trained on clean room procedures, machine operation, gown and personal protective equipment wear and techniques to troubleshoot equipment should there be an issue on the fill and finish line. This industry is incredibly specialized from the personnel required to the materials needed, and both are in short supply.

The Columbia University Capstone team aims to illuminate the fill and finish manufacturing process by providing an unbiased assessment on the scalability of a vaccine meant to inoculate billions of the world's populations and to help the public better understand realistic timelines for vaccine distribution. Given the need for scalability, we assess that we must undertake public-private partnerships in order to meet the demand and need for a COVID-19 vaccine.

Transparency is our watchword. This project is only the beginning of the discussion and will provide our stakeholders with information and insights from the industry and questions for further research. We will raise as many questions as we've discovered answers for and call into question some of the policies and procedures surrounding vaccine manufacturing. We recognize that we do not have all of the answers. The more information we provide, the better prepared we are to address future challenges in the COVID-19 pandemic and ultimately be better prepared for emergency and contingency planning, education, communication, and policy decisions in future public health emergencies.

Areas for Further Research:

As the world begins to inoculate their populations, various issues and gaps in the vaccine supply chain process have come to light. While some countries have used their limited resources to ensure every drop of vaccine is used, other countries have demonstrated that the lack of distribution planning and complications of inadequate cold storage are creating waste to an already scarce resource.

United States President-Elect Biden formed a COVID-19 Task Force with the stated goal to reinforce mask use, administer 100 million vaccines and help children get back to in-person education. A notable gap in this task force is a representative from the vaccine manufacturing industry. This is an oversight that cannot go unnoticed, and is also indicative of the President-Elect's desire to keep big industry out of policy decisions. Unfortunately, this is a time when the vaccine manufacturing industry must be involved in the planning. Without this expertise, vaccine production and distribution will continue to be an insurmountable challenge for the United States.

As the United States and the rest of the world reels from the economic crisis, policy makers must look at using small business grants to incentivize contract manufacturers to produce COVID-19 vaccines or to move money to logistics companies that can focus on storing the vaccines in the appropriate locations at the appropriate temperature. It has also become clear that technical training through junior colleges or technical schools that specialize in the skills needed to facilitate the COVID-19 vaccine distribution is a real demand. People must be incentivized to enter these fields and schools must be given government funding to create pathways to meet this need.

Finally, a notable gap illuminated by the initial COVID-19 vaccine rollout is the lack of capacity at fill and finish facilities and distribution sites. This report will address some of these challenges but what has become more evident is the lack of planning that went into the actual distribution of the COVID-19 vaccines. Manufacturers know the exact amount of vaccine they produce, the amount of people that can be inoculated with those doses and how the cold-chain process and storage works. It appears that this information is not making it to the end users or policy makers who are creating distribution plans. The data exists; and with this data industry professionals

should be able to predict shortages and propose plans for larger facilities, especially in essential hubs around the United States.

National action is essential to ensure that the proper facilities exist and are properly equipped and manned. This industry needs to let go of the grip on proprietary information and look to the greater good. The United States specifically can learn a lot from how the rest of the world is approaching the COVID-19 vaccine problem. These lessons must be shared to ensure that the pandemic has a realistic and predictable timeline for its end.

II. The Vaccine Production Process - Where is Fill and Finish in the Vaccine Supply-Chain?

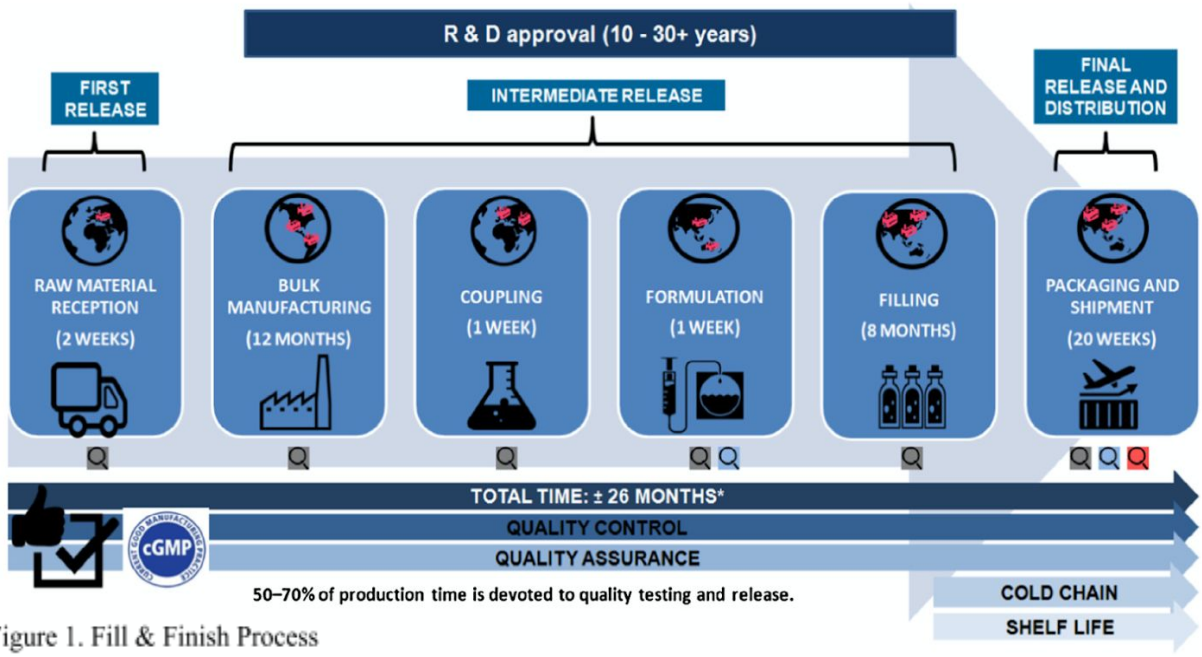


Figure 1. Fill & Finish Process

The above diagram depicts the vaccine supply-chain. In normal times, drugmakers begin bulk manufacturing the drug substance, i.e., the primary ingredient in the vaccine, after the vaccine shows efficacy and safety in clinical trials, but these are not normal times. Drug makers began mass-producing the active pharmaceutical ingredient (API) and filling it into vials even before clinical trials were complete, taking the risk that the product would never be authorized by regulatory authorities. The total time it normally takes to bring a vaccine to market is approximately twenty-six months, a minuscule amount of time compared to the ten to thirty-plus years of research and development that goes into a new vaccine. Yet, Pfizer/BioNTech and Moderna developed vaccines with efficacy rates above ninety percent (90) in a matter of months.

Once developed, the drug substance is bulk manufactured, transported to another manufacturing facility for the formulation, and filled and finished before it is ready for distribution.

Vaccine Formulation

Some manufacturing facilities formulate the vaccine, while others do not. The formulation consists of mixing and blending the active pharmaceutical ingredient (API) with buffers, adjuvants, and other product components to produce the final drug product.[1] The formulation process requires sophisticated intricate machines which have to be tailored to the specific product. Facilities without the capability to formulate the vaccine may purchase the vaccine already formulated.

Aseptic Fill and Finish: Glass Vials

Fill and finish consists of the filling, stoppering and capping of a vial, and the inspection, labelling and packaging of the vial.

I. Filling is the process in which the vaccine is filled into the vial in an extremely high-quality environment known as the critical zone. The critical zone must meet regulations which stipulate the number and size of the particles that can remain in the air. The inspection phase is critical because even with the use of High Efficiency Particulate Air (HEPA) filters, some particles are bound to remain in the environment. For more information regarding protection of the critical area and air quality control refer to appendix E.

   Liquid filling machines are custom-designed to ensure dose fill accuracy and dose homogeneity across vials. Dose fill accuracy is influenced by the filling speed, product viscosity and product foaming potential.[2] Because dose fill accuracy is impacted by the nature of the product, filling machines have to be tailored to the specific product.

II. Stoppering is the process where the rubber stopper is inserted into the neck of the vial. This operation takes place in the same quality environment as filling, occurring as soon after filling as possible to reduce the chances of contamination. For lyophilized products, the stopper is only partially inserted. The lyophilization process--i.e., freeze-drying which reduces a vaccine to a powder which is more stable than the liquid form--occurs through the partially inserted stopper. Immediately thereafter the stopper is fully inserted, sealing off the vaccine from the surrounding environment. The following diagram depicts a sterile stopper bag attached to an isolator: the rubber stoppers are transferred to the stoppering device where they are inserted into the neck of the vial.

[1] Wiker, George. Sterile Manufacturing Facilities. *Good Design Practices for GMP Pharmaceutical Facilities.* 2017.

[2] Akers, Michael. Sterile Drug Products. *Baxter BioPharma Solutions.* 2010.

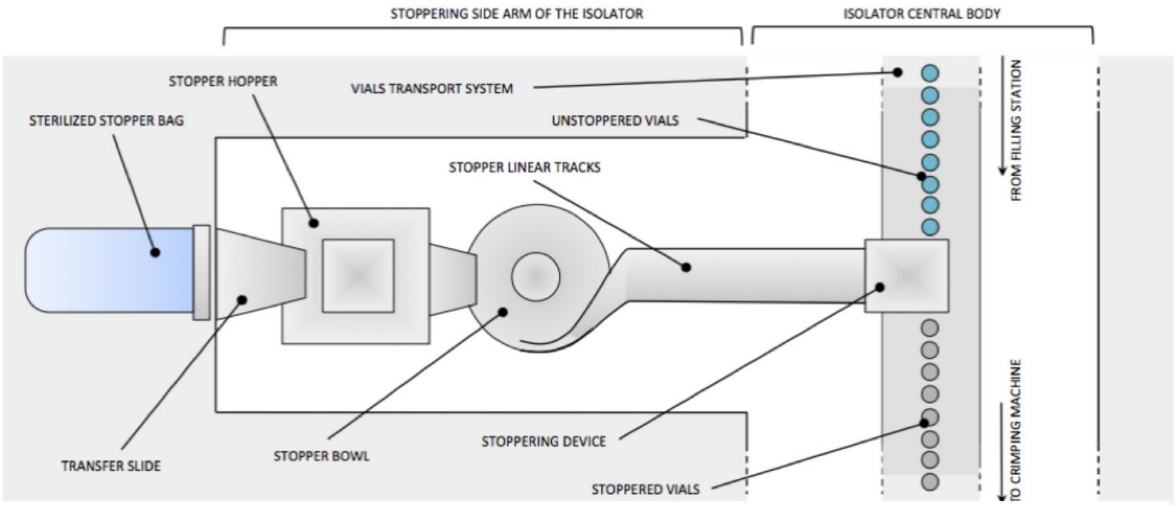


Figure 2. Top view of the stoppering part of an isolator

Source: Design of aseptic filling machines will change after recent update of GMP Annex 1. October 7, 2019.

III. Capping is the process where an aluminum crimp cap is crimped onto the mouth of the vial, sealing the rubber stopper in place. The capping operation is conducted at the capping station, which may be a lower quality environment than the filling and stoppering stations because the vaccine has already been sealed off from the environment.

IV. Vial inspection consists of identifying visible particles in the vial or cosmetic issues such as chipped glass. Vials with these issues are discarded, and depending on the prevalence of the issue, investigations into the cause may be necessitated. Vials are often manually inspected, but automated systems using light and computer imaging can also be used.

V. Labeling consists of patching a label onto the side of the vial which has information such as the dose quantity contained in the vial, the dose to be administered to the patient, the vaccination schedule, as well as how the vaccine is to be administered. Finally, the vials are stored in temperature-controlled environments or packaged in preparation for shipping. For large-scale production, machines perform labeling and packaging.

The fill and finish of a vaccine is an aseptic process, i.e., the vaccine, vial, stopper and cap are each sterilized in independent procedures and then brought together under the extremely high-quality environments described above. The vaccine sterilization process is typically performed by passing the vaccine through a 0.2-micron pore-size sterile filter, but the filter needs to be selected for the specific vaccine being processed because the filter can damage the vaccine. The sterile vaccine will then come in direct contact with tubing/piping, the filling needle, the environment, the glass vial, and the rubber stopper, and thus each of these need to be free of microbiological, particulate or pyrogenic contamination. The following diagram depicts the

aseptic processing of vials in which the active pharmaceutical ingredient (API), vials, stoppers and caps are sterilized in a Grade A area, i.e., an environment with less than 3,520 particles with a diameter of 0.5 microns or larger, and then filled, stoppered, and capped in a Grade A area. For a comparison between aseptic processing and another common approach to fill and finish known as terminal sterilization refer to appendix E.

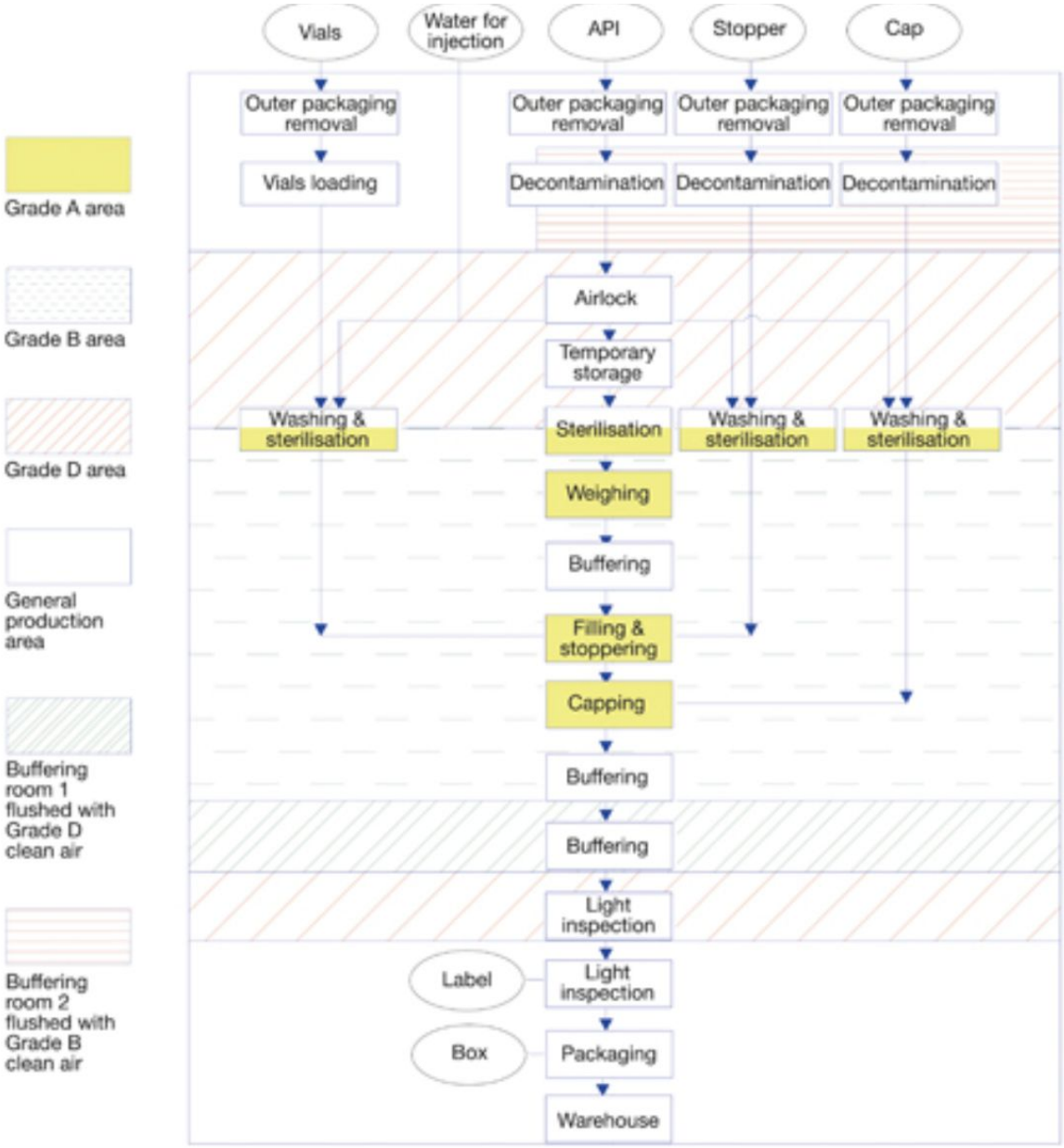


Figure 3. A process flow diagram for the facility

Source: Designing facilities for aseptic filling. https://www.cleanroomtechnology.com/news/article_page/Designing_facilities_for_aseptic_filling/86450. February 27, 2013

Vial Preparation

A vial is a glass container that can be used to hold a vaccine throughout manufacturing, transportation, storage, and use.[3] Some manufacturing facilities wash and sterilize vials in preparation for filling, but vials can also be purchased ready-to-use. In-house preparation consists first of washing with a sterile, non-pyrogenic water known as Water for Injection (WFI) in linear or rotary washing machines which use needles or jets to spray the WFI into inverted vials. In one design, the washing machine is integrated with a sterilizer which moves the vials on a conveyor belt through a tunnel set to at least 250 degrees Celsius with the function of killing all microbiological life and destroying all endotoxins. A design in which the washing and sterilizing machines are not integrated within the fill line requires the vials to be manually moved to the fill line, which creates a contamination risk. The following diagram depicts a tunnel sterilizer: the vials move from left to right against HEPA filtered air toward the filling station. For a more detailed description of in-house vial preparation refer to appendix E.

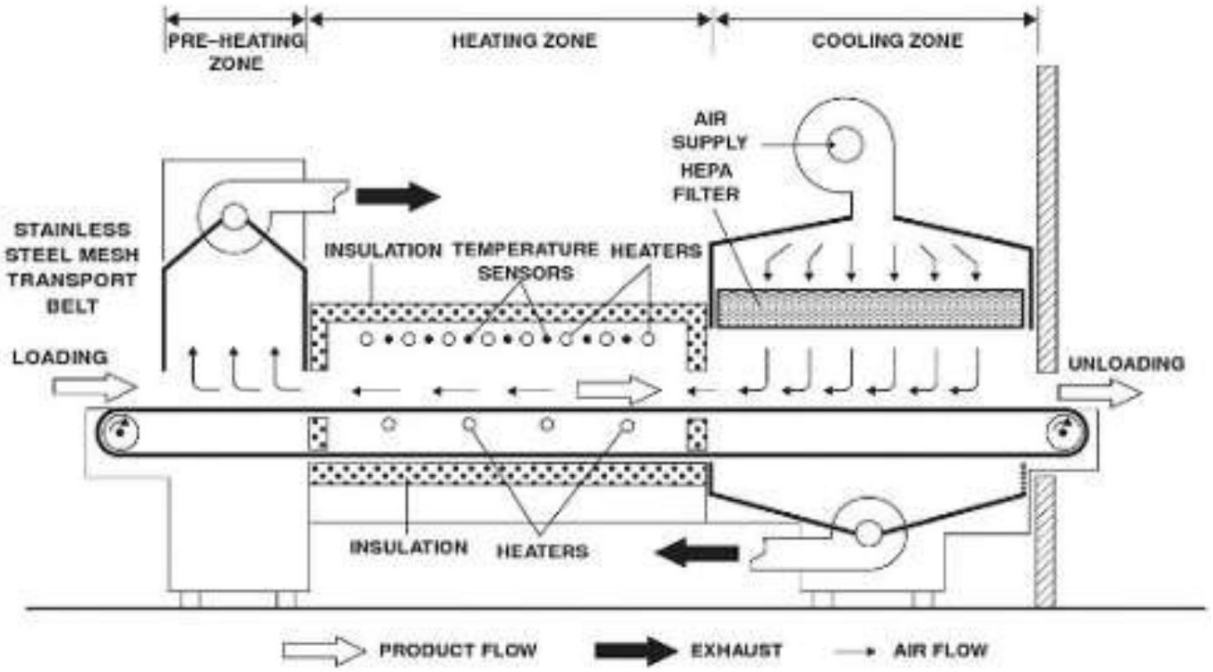


Figure 4. Dry heat sterilization / depyrogenation tunnel. Schematic (Akers, 2010)
Source: Voicu, Gheorghe, et al. Aspects Regarding Aseptic Packaging. 2017.

Rubber Stopper Preparation

Rubber stoppers are cylindrical rubber objects which are inserted into the neck of the vial after it is filled with the vaccine. Some manufacturing facilities prepare rubber stoppers in-house. The

[3] Fran DeGrazio and Lionel Vedrine, "Quality by Design for Primary Container Components," in *Quality by Design for Biopharmaceutical Drug Product Development*, ed. Feroz Jameel et al., AAPS Advances in the Pharmaceutical Sciences Series (New York, NY: Springer, 2015), 365–401, https://doi.org/10.1007/978-1-4939-2316-8_17.

depyrogenation process removes all pyrogens from the stopper by rinsing with copious amounts of hot WFI. Some rubber stoppers then require the application of silicon, which is a lubricant used to ensure that the rubber stoppers move easily during production. The rubber stoppers are then sterilized in an autoclave which uses steam to kill microbiological contaminants. The rubber stoppers must be free of pyrogens and microbiological contamination because they come in direct contact with the vaccine in the vial. For a more detailed description of in-house rubber stopper preparation refer to appendix E.

Filling glass vials with a vaccine construction in a sterile environment may sound simple, but in reality, it is a highly complex and technical process with almost no margin of error. In the following section we have identified 6 potential challenges that may hinder a newly established vaccine manufacturing facility, or an existing facility that wishes to significantly scale up its production capacity.

II. Gaps and challenges

Challenge 1: Tailored manufacturing process - limits large scale production

As mentioned in the previous section, the facility design in a fill and finish facility requires dozens of equipment types from dozens of suppliers across the world, specialized personnel and an abundance of safety and protocol checks throughout the process. There is also a difference between these factors if there is an existing facility which needs to be adjusted for a COVID-19 vaccine or if a new fill line is built in a facility.

Reorienting an Existing Fill Line for COVID-19 Vaccines

One of the greatest barriers preventing a company from reorienting an existing fill and finish facility to produce a COVID-19 vaccine is scheduling. Contract manufacturers are obligated to fill existing batches of other pharmaceuticals and must negotiate with their clients in order to shift focus to a COVID-19 vaccine fill only. In some cases, a pharmaceutical company may have a stockpile of their drug or vaccine in storage and are able to halt further production for a time. However, this is also dependent on the shelf life of those existing products and the company's business model. Another consideration is if the fill line needs to be reoriented from a drug like insulin, to a virus vaccine. Those two products cannot be filled in the same facility, and a vaccine requires additional safety and quality control protocols to ensure the efficacy and safety of the vaccine. Moreover, many vaccines are annual (like influenza) and the fill lines only operate for four months out of the year using faster equipment. Although there are now two COVID-19 vaccines approved for use in the United States, there are still questions about dosage of the vaccine and uncertainty about these vaccines becoming annual instead of a one-to-two-time use. Scaling these facilities to meet the needs and demands of the public cannot be done overnight.

Manufacturers also need to have a desire to scale. Industry experts suggested that some sites, particularly in Germany, do not necessarily want to scale up production of their facilities even if they could profit from the current COVID-19 vaccine manufacturing process. Most of these facilities are in small towns and are family-owned companies and likely do not have the capability to scale even if they had the desire. They are more comfortable being a small company and adhering to timelines that they adopted from years before. Because not all manufacturers are willing or able to adapt to the scaling requirements, one can assume that the burden will fall on larger companies who are able to scale - but this burden also promises large profits as the world rolls out the first batches of the COVID-19 vaccines.

Challenge 2: Lack of Trained Manpower

Aseptic processing and sterile fill-finish is a uniquely challenging area that requires the close coordination and complex interaction between highly trained personnel, sterilized product, the manual fill-finish equipment system, cleanroom and support facilities and sterilized filling components. Contamination of the product, whether it be from microorganisms or particulates, is the worst nightmare, and failure in providing adequate training to the workers in the facility can lead to catastrophic, even life-threatening, consequences. From the layout of the cleanroom, to the flow of personnel, to the preparation of equipment, to the lyophilization and stoppering processes themselves, the aseptic fill and finish process of the vaccines entails many more risks than traditional drug manufacture.[4] At any stage of the process, a single moment of contact with a non-sterilized worker, tool or draft of air could render an entire batch of product unusable and require the process to be restarted from the beginning. Therefore, workers on the fill and finish production lines are required to have heightened attention to detail, ability to address every material, component and stage involved in the process.

It is not enough to only consider the actual production workers; experts in microbiology, lab workers, technical support personnel and quality assurance experts are all required to operate a fill and finish facility safely and within regulations. These highly specialized personnel all must be familiar with vaccine batch records and be able to spot any irregularities coming off of the fill line. Together this team assures the manufacturer that the vaccine batch is safe and free of contamination and ready for storage or transport to a different facility. As mentioned previously, the fill and finish manufacturing process are tightly controlled and require management that can keep to timelines and not over-promise production quotas to their clients. Even with the largest and most efficient fill line that has all of its required personnel and equipment, it's important to note that any facility is limited to four critical factors: *time, personnel, equipment capacity and capability and storage.*

[4] Sterile Fill Finish, March 9th, 2018, Adare Pharma Solutions, Available at: https://www.contractpharma.com/issues/2018-03-01/view_features/sterile-fill-finish/

Based on a conversation with industry experts, contract manufacturers usually hire production workers who already have experience working on a fill and finish line. These production workers tend to move from company to company so there is generally a pool of available workers in regions where there are manufacturing facilities. Once a company hires their production workers, these personnel must be certified in various capabilities unique to an aseptic fill area. Some of these requirements include gown certification, which must be recertified every six months to a year. The current pandemic demands a rapid scale-up in the manufacturing capacities among the fill and finish contract manufacturers, which resulted in a massive shortage in supply of experienced workers who are qualified to participate in the fill-finish manufacturing operations. The industry standard for the training process takes roughly around six months, but due to the current pandemic, companies are attempting to speed up the hiring process while providing training and technical assistance to the new staff to accelerate operational readiness. However, to ensure each newly added worker receives adequate training under shortened time is a challenging task.

Our industry experts have also pointed out that the pharmaceutical industry as a whole lacks adequate manpower in the manufacturing and operational space. And in the long run, if another pandemic like Covid-19 strikes the world again, we will need policies that can incentivize citizens to pursue pharmaceutical manufacturing and operational careers ahead of the next crisis. He used the example of Puerto Rico's tax breaks for pharmaceutical companies in the 1970s, when the universities in Puerto Rico responded by providing relevant degrees and certifications that were able to supply the trained personnel to support the pharmaceutical industry. These degrees and certifications were not only for those that invent medicines, but also for those who are engaged in the manufacture, operation, and distribution of medicines. Even if the tax breaks had ended two decades ago, and the infrastructures in Puerto Rico have disintegrated, there are still many Puerto Ricans scattered across the pharmaceutical industry in the world as the result of the policy from half a century ago. The industry expert we spoke with suggested that there should be policies that can ensure the pharma industry not only have the people that are inventing new medicines, but those that are capable of using the equipment and technology invented.

Challenge 3: Financial Restrains

Challenge in Commercialization

There is a lack of financial incentives for firms to build and expand their capacities. Typically, pharmaceuticals companies prefer to invest in chronic disease treatment than acute diseases because it is more profitable, and the investment return is guaranteed. For example, treatment for diabetes is a guaranteed revenue for at least 10 years from each patient, but for a disease like Covid-19, it is uncertain how likely it is to reoccur in the future. This could mean that any equipment or investment made for the scaling of production might not be useful next year. The industry expert we talked to confirmed that it can cost hundreds of millions to just retrofit the

facility to expand their capacity. And we are not talking about the several well-known pharmaceutical companies, but many of the smaller manufacturers, that are often squeezed in profit by the bigger companies and have very limited cash on hand. So, it's extremely difficult for them to invest millions of dollars without foreseeing the proper return on investment. One mistake and they can go bankrupt.

Last year, there was a chain of bankruptcies among antibiotics developers in the U.S. when they were racing to find a cure for the superbug infection which is resistant to all known antibiotics.[5] But the drug they developed is a 10 day treatment, and it cannot generate enough revenue to cover their R&D expenses.[6] At the moment, the government has been collaborating with the pharmaceutical companies and vaccines developers by providing them contracts and grants, yet we hear very little about the much-needed financial support for the smaller manufacturing companies at the mid-to downstream of the supply chain. Therefore, public-private partnerships are essential to finance the construction or expansion costs of fill-finish facilities, to ensure that smaller players won't be at risk of going under after the pandemic is over.

Covid-19 Vaccine Gamble: The Governments could be betting on the wrong actors

The Covid-19 vaccine development is a lottery played on an unprecedented scale. There are 321 potential vaccines in development globally. Governments around the world are betting on the innovators, the hundreds of vaccine developers by putting contracts together and paying them upfront for millions of doses of vaccine candidates that have not yet been proven to work. Governments are betting on multiple vaccine developers to build a portfolio and preparing that not all of the vaccines in the late-stage development will make it through. The U.S. currently ordered 800 million doses of potential Covid-19 vaccines from six companies, and the UK has ordered a total of 340 million doses of potential Covid-19 vaccines from six different vaccine developers. But at the end of the day, among those leading vaccine developers that had received governments' contracts, nobody knows which vaccine developers would create the vaccine that show efficacy, be licensed, and be recommended for use, and only a handful of those developers will succeed. Earlier in December 2020, the Covid-19 vaccine candidate developed by Oxford and AstraZeneca was paused after a volunteer became ill. Despite the candidate eventually passing the review, and is currently authorized for emergency uses, there is still a high chance that some governments could have backed the wrong horse, and have rolled the dice and do not know whether the gamble will pay off.

According to Gavi, vaccines at the preclinical stage have approximately a 7% chance of succeeding, while the ones that make it to clinical trials have about 20% chance.[7] Our industry

[5] Jacob, Andrew. Crisis Looms in Antibiotics as Drug Makers Go Bankrupt, December 25, 2019, NY Times. Available at: https://www.nytimes.com/2019/12/25/health/antibiotics-new-resistance.html
[6] Ibid.
[7] https://www.theguardian.com/world/2020/sep/11/the-covid-19-vaccine-gamble-where-bets-have-been-placed-and-why

experts shed light on what the government should be doing: instead of betting on the vaccine development that has a small chance of success, governments should divert a portion of the fund to put in place the manufacturing facilities that any innovators would need regardless who wins. If governments would bet on the vaccine product manufacturing process, they only need to bet on two different types of platforms: *1. Live-virus vaccine filling lines; 2. Non-live virus (standard) vaccine filling lines.* Regardless which vaccine developer wins the race and makes it to the end, it will need one of the two platforms to manufacture its vaccines, a 50% chance of success. In the long run, strategically, there should be enough standby vaccine manufacturing capacity invested by the federal government, as idle capacity could be extremely expensive for private firms to keep. In this way, no matter which of the innovators succeed in vaccine development in the face of the next pandemic, there will be enough vaccine manufacturing capacity for the population.

Challenge 4: Limits in Supplies

Building a New Fill Line in an Existing Facility

Building a new fill line requires well over a year of planning, scheduling, resourcing and training in order to make the fill line operational. Before any purchases or plans are made a manufacturer must work with engineers to determine space requirements, the business team to determine funding and other resources and potentially with existing clients to propose a joint funding venture into building a new fill line. Once the manufacturer determines that they have the space and resources to complete the project, leadership must determine whether they want to halt production on their existing line or if they want to continue production. Since halting production is highly unlikely, experts must create a plan to keep the facility clean while one line is still operating 24 hours a day, 5 days a week and construction is occurring on the new line.

Once the manufacturer creates this plan the appropriate personnel create risk assessments, meet monthly to discuss updates and facility specifications and then determine who they will partner with to complete construction. The construction element is not straightforward, largely because they are required to work hours outside of normal business hours and they need to understand hospital vs. pharmaceutical grade construction. This skill-set is highly specialized but is more common in regions where manufacturers are abundant. A manufacturer will also prefer a construction company that has experience building a fill and finish facility.

One contract manufacturer provided an example of the timeline to build a new fill line; the process began in 2017 and the manufacturer completed the fill line in the summer of 2020. In this particular case, the contract manufacturer spent a year writing specification for the fill line. After completing the specifications, they began the process to complete purchase orders with vendors; this process took about six months to complete. By the spring of 2018 all items were ordered, and shipping of items began two months later, but they did not receive all of the equipment until the spring of 2020. The bulk of the construction and build of the fill line took

about six months to complete while the company waited on other specialized equipment. Interestingly, there is not one location where the specialized equipment is purchased from. Items like fillers and isolators are generally only available in Europe - specifically Germany and Italy, while other items like boilers and autoclaves are available anywhere in the world and if they can be purchased in the United States, that is the preferred option. Throughout the purchasing and build of the fill line, all departments in the company are involved. The legal team ensures that all specifications are met to meet FDA regulations, the scientific departments ensure that the equipment is appropriate for the pharmaceutical type and engineers and production managers ensure that the facility will withstand strict cleaning regimes and sterilization procedures.

Syringes

Syringes are cylinder-shaped tubes that contain plungers which push the liquid drug or vaccine product through a needle. The cylinder-shapes tubes of syringes are typically made of glass, plastic, or stainless steel, however, for vaccinations they are largely made from plastic. Syringes are manufactured for vaccine administration in one of three ways: needleless prefilled glass syringes, empty glass syringes, and empty glass syringes accompanied by the vialed vaccine/drug. The syringe manufacturing process, as well as the in-house preparation and sterilization of the syringe, usually takes between 12 to 18 months, posing a significant barrier to the manufacturing and distribution of COVID-19 vaccines.

The United States currently produces an average of 665 million syringes per year, with an estimated 850 million needed for the distribution of COVID-19 vaccines alone. With a national stockpile of only 15 million syringes, the United States faces a syringe shortage critical to the distribution of COVID-19 vaccines despite the recent increased funding for supply manufacturing. This looming shortage posed by manufacturing shortages threatens the rollout of COVID-19 vaccines and the continuation of medical services which require syringes, vials and rubber stoppers, necessitating a national and international coordination for the production and sterilization of vaccine supplies.

Vials

Vials are small, tubular glass containers that contain drug or vaccine products. They are typically made from Type I Borosilicate glass and are manufactured for vaccine administration in one of two ways: single-dose vials or multi-dose vials. The latter provides a significant advantage to the manufacturing process as one vial can be used for up to ten doses of a given vaccine, while syringes can only be used once in order to prevent cross-contamination. The manufacturing process for vials requires the production and sterilization of vials, which typically takes less than 12 months. A major glass vial producer, Schott, has received requests for more than 1 billion glass vials from pharmaceutical companies including Pfizer and AstraZeneca, with the company only having the capacity to manufacture 500 million in one year. Despite the quicker production rate in comparison to syringes, there is still the threat of a national and global shortage of glass

vials as manufacturers scramble to produce the 1.2 billion vials needed for vaccine distribution in the upcoming year. For more information on what it takes to make a vial, the vial manufacturing process, and the vial supply chain, refer to appendix E.

One report provided by the FDA in May 2020 estimated that the glass vial shortage in the United States could hamper the national vaccine rollout by up to two years. Operation Warp Speed, led by the US Department of Defense and the Department of Health and Human Services, has taken on the challenge of upscaling manufacturing of glass vials to prevent a shortage in the upcoming vaccine rollout. The Operation has provided more than $200 million to companies Corning and SiO2 to produce an additional 164 million glass and glass-coated vials for COVID-19 vaccines. However, with an estimate of at least 8 billion glass vials needed for a global rollout, international efforts and cooperation are vital to the success of distributing the upcoming COVID-19 vaccines and ensuring the continuation of medical services reliant on the product.

Challenge 5: Operational challenge - Lack of transparency in Manufacturing Capacity

Lack of transparency in the manufacturing capacity

Fill-finish process is the last mile and the major hurdle on the path to vaccine distribution, which is a complex operation that many pharmaceutical companies outsource to third-party service providers called contract manufacturers (CMOs). One serious challenge identified in the fill and finish process is the lack of transparency in the manufacturing capacity. As vaccines developers have been locking up fill -finish manufacturing capacity from contract manufacturers, it is unclear how companies will coordinate and plan to manufacture the promised number of vaccines given the lack of visibility in the fill-finish manufacturing process.

Complexity in assessing manufacturing capacity

According to one industry expert, it is almost impossible to accurately assess the yearly manufacturing output of any fill-finish manufacturing plant because many factors can influence that result. The first factor is the vaccine itself. Depending on the type of bulk vaccines, the efficiency of the fill-finish process can vary significantly. Therefore, the accurate estimation of the production output of a certain vaccine will not be completed until six months of the production is in operation. This adds additional complexity in assessing the potential manufacturing capacity under the current pandemic. Given the varieties of vaccines that are currently being developed, it is highly likely that each type of vaccine will require a very different time-frame to be filled.

Proprietary knowledge on the manufacturing processes

In addition, firms withhold information on their manufacturing process as proprietary. Earlier in June 2020, Inovio, a vaccine developer based in Philadelphia sued its contract manufacturer

VGXI, because Inovio claimed that VGXI does not have the manufacturing capacity to produce the quantity of the vaccine Inovio required.[8] Then VGXI countered that Inovio was seeking information on its manufacturing procedure which is 'proprietary'. However, this information on the manufacturing process of one manufacturing plant is essential at determining the efficacy of the production at certain facilities. Lawsuits arise after developers sign contracts with CMOs and question if the CMOs have the capacity to produce the promised amount. When the developer tries to get that information from the CMO, the CMOs is often restricted to share that information due to its proprietary nature.

Overlapping web of contracts

Fill-finish manufacturers have contracts with multiple vaccine developers, but there is no evidence that they can fulfill their contractual obligations. At present, Emergent BioSolutions (a CMO) have signed a contract with Johnson & Johnson to produce 750 million to 1 billion doses in 2021, they have also signed contracts with other developers, which adds up to at least 1.5 billion doses for next year to produce. However, according to the senior vice president of the business unit at Emergent, she stated that the Bayview facility, one of its largest facilities, has the capacity up to 300 million annually. It is unclear how these contracts line up with Emergent' actual capacity.

Potential Geopolitical issues

Geopolitical challenges could arise in the future as well. One manufacturing facility has plants in other countries, then will the offshore facility be able to ship the vaccines produced there back to the U.S. where it is headquartered? These are questions we need to ask because there are many factors at play that complicates this process.

Therefore, to make sure we can have enough vaccines provided to the people, it is essential that the US federal government can stand out and coordinate the vaccine production efforts. The federal government has the ability to complete a comprehensive assessment of manufacturing capacities of all U.S. CMOs, but unfortunately, there is no plan/announcement on such coordination effort at the moment.

Challenge 6: Regulatory challenge - New facilities require an extensive documentation for EMA/FDA approval

Obtaining EMA/FDA approval is an important milestone for every vaccine manufacturer, but it is also a lengthy and costly process for all involved. This is especially true for first time applicants as individual manufacturing processes corresponding to each new drug product must be approved separately, hence long-standing facilities can establish a documentary record of their previous manufacturing process in the regulatory agency prior to their applications.

[8] Hargreaves, Ben. *Lawsuit Accuses CDMO of 'blocking' Covid-19 vaccine*, June 8, 2020, BioPharma Reporter. Available at: https://www.biopharma-reporter.com/Article/2020/06/08/Inovio-sues-VGXI-over-COVID-19-vaccine

Documentation of the entire manufacturing process and every quality control system in place can easily become a daunting task in and of itself. Manufacturers are also required to conduct a "media fill" simulation consisting of 3 separate "Process Performance Qualification" batches as a prerequisite for FDA approval, which can add additional time necessary for preparing the application.

Fortunately, both EMA and FDA have put in place various forms of expedited procedures designed to speed up the application process, with the goal of ramping up vaccine production as quickly as possible. Although these procedures mainly reduced the allotted time for each step of the review process and does not waive any actual requirements for documentation. This arguably benefits existing manufacturers the most, as an application can be fast-tracked through the process with the help of existing documentation and continued process verification. First time applications, however, will still face similar challenges obtaining EMA and FDA approval for their manufacturing facilities.

III. Regulatory Framework

Vaccine production and manufacturing, as a process leading to biological medicinal products, requires a diligent and efficient regulatory framework. Due to the risks entailed in the manufacturing process, ranging from cross – contamination to environmental implications, as well as the sanitary impact of vaccines, the control thereof frequently demands biological analytical techniques, which have a greater degree of variability than physiochemical determinations.[9] To this effect, both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA or EMEA) are responsible for the application and enforcement of a detailed monitoring system with respect to the safety and mitigation of risks revolving around vaccine manufacturing. The following section will focus on and analyze current regulatory practices within the European Union and the United States, respectively.

1. Introduction to the EU Regulatory Framework on Vaccine Manufacturing

In terms of EMA regulation, a clear and brief overview of the overall mechanism of vaccine authorization is required. Pursuant to the provisions of Article 6 of the Directive under No. 2001/83/EC,[10] "no medicinal product [for human use] may be placed on the market of a Member State unless a marketing authorization has been issued." In essence, the marketing authorization comprises the major regulatory approval which is issued at a Union level with respect to a vaccine that is to be distributed within the EU. The aforementioned authorization is issued

[9] Emily P. Wen, Ronald Ellis and Narahari S. Pujar, *Vaccine Development and Manufacturing*, John Wiley & Sons, Inc., Hoboken, New Jersey, 2015, pp. 396
[10] Directive 2001/83/EC

centrally by the European Commission[11] in the name of the vaccine *producer*, namely the developer thereof. Consequently, a vaccine developed by Pfizer or AstraZeneca shall receive a marketing authorization in the name of said pharmaceutical companies, regardless of whether the latter manufacture the doses of the vaccine themselves or enter into manufacturing agreements with third parties, acting in such capacity. On this basis, the major regulatory agencies, including the EMA, have adopted an approach which dictates that the "method" used for manufacturing is inextricably linked to the product itself, hence it is subject to the review and careful monitoring thereof [12]. The aforementioned method includes the manufacturer's facility, relevant equipment, processing parameters, employed personnel, environmental implications and several other components which shall be further explored below. Therefore, the marketing authorization, which is issued in the name of the pharmaceutical company, *extends* to the *means* employed for the vaccine to be manufactured, e.g., the manufacturing facilities, the respective processes, quality control et al. Consequently, the above may be summarized: *for a vaccine, i.e., the product, to be authorized by means of a marketing authorization, all the components regarding the manufacturing thereof, i.e., the process, must be approved by the competent regulatory agency*. The foregoing extension of the marketing authorization to the overall manufacturing process of a vaccine maintains its effect regardless of the country in which the manufacturer is incorporated or established. Indeed, as long as the final product is going to be placed in the market of an EU Member State, the vaccine producer needs to be provided with a marketing authorization by the EMA.

Although part of the pharmaceutical companies developing vaccines are also the manufacturers thereof, a substantial number of them enter into agreements with third – party contractors which undertake (part of) the manufacturing process on their behalf.[13] For the purposes of the report herein, the following sections will treat the "manufacturer" of a vaccine as an independent, third – party contractor which undertakes the contractual obligations set forth in the agreement entered into with the vaccine developer.

2. Guidelines on Vaccine Manufacturing and Good Manufacturing Practice (GMP)

The Commission Directive under No. 2003/94/EC[14] (hereinafter, also referred to as the "GMP Directive") sets forth the principles and guidelines with respect to Good Manufacturing Practice (hereinafter, also referred to as "GMP") regarding medicinal products for human use and investigational medicinal products for human use. Per the provisions thereof, vaccines fall within

[11]Obtaining an EU marketing authorization, step - by - step, available at: https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/obtaining-eu-marketing-authorisation-step-step#european-commission-decision-on-the-marketing-authorisation-section

[12] Emily P. Wen, Ronald Ellis and Narahari S. Pujar, *Vaccine Development and Manufacturing*, John Wiley & Sons, Inc., Hoboken, New Jersey, 2015, pp. 396

[13] *COVID – 19 Vaccine Makers Tap Contractors to Produce Billions of Doses,* available at: https://www.wsj.com/articles/covid-19-vaccine-makers-tap-contractors-to-produce-billions-of-doses-11608373800

[14] Directive 2003/94/EC

the scope of the aforementioned Directive and their manufacturers are, therefore, subject to GMP obligations. Pursuant to the definition[15] of the directive, good manufacturing practice means "the part of quality assurance which ensures that products are consistently produced and controlled in accordance with the quality standards appropriate to their intended use." In this context, GMP provides for several obligations towards the following main sectors: quality assurance system,[16] personnel,[17] premises and equipment,[18] production[19] and quality control.[20] Aiming at the facilitation of the respective manufacturing companies, and on the basis of Article 47 of the EU Directive under No. 2001/83/EC, the EU Commission has issued several guidelines which provide guidance and interpret the principles laid down in the GMP Directive.

2.1. Quality Assurance System

Pursuant to Article 6 of the GMP Directive, each manufacturer is under the obligation of establishing and implementing a pharmaceutical quality assurance system, in which both the management and personnel of various departments shall actively participate. In essence, GMP dictates that the manufacturer must have in place a system, by virtue of which the production, control operations and managerial responsibilities are clearly specified, product and process knowledge is managed throughout all lifecycle stages, and processes are in place to assure the management of outsourced activities.[21] In this regard, a fully structured and absolutely documented system is required, by virtue of which there is a standard process at each level of production and all responsibilities are clearly allocated among top management and personnel.

2.2. Personnel

The major principle that the Personnel Guideline[22] intends to implement is that each manufacturer must have an adequate number of personnel, which is necessarily qualified, and has sufficient practical experience. More precisely, the manufacturer must have permanently and continuously at their disposal the services of *at least* one qualified person who accumulates the following three (3) characteristics.[23] First, he/she must be in possession of a diploma, certificate or degree awarded upon completion of a university course of study, lasting at least four (4) years, in pharmacy, medicine, veterinary medicine, chemistry, pharmaceutical chemistry and technology, biology. Furthermore, this individual will be responsible to ensure that the medicinal

[15] Art. 2 No. 6 of the Directive under No. 2003/94/EC
[16] Art. 6 of the Directive under No. 2003/94/EC
[17] Art. 7 of the Directive under No. 2003/94/EC
[18] Art. 8 of the Directive under No. 2003/94/EC
[19] Art. 10 of the Directive under No. 2003/94/EC
[20] Art. 11 of the Directive under No. 2003/94/EC
[21] The Rules Governing Medicinal Products in the European Union, Volume 4, *EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use*, Chapter 1, Pharmaceutical Quality System
[22] The Rules Governing Medicinal Products in the European Union, Volume 4, *EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use*, Chapter 2, Personnel
[23] Article 48, 49, 51 Directive 2001/83/EC

products have been manufactured and checked on the basis of the marketing authorization and the laws of the country in which they were produced. Finally, in case of products coming from third countries outside the EU, the aforementioned person must ensure that these have undergone in a member-state full qualitative analysis, quantitative analysis of active substances, and all other requisite tests, pursuant to the marketing authorization. In practice, most manufacturing companies employ a significant number of people with the above qualifications, so that all regulatory requirements, in addition to those deriving from the marketing authorization are adhered to.

With the intention of realizing the foregoing concept, the guideline suggests the implementation of an organization chart that demonstrates and clarifies the relationships between the Head of Production, the Head of Quality Control and the Head of Quality Assurance, if applicable, in a managerial hierarchy. The latter is essential both in terms of responsibility undertaking and allocation of tasks among the relevant departments. For the sake of these purposes, the guidelines indicate the most fundamental responsibilities of each managerial department. In this respect, the Head of Production and the Head of Quality Control are expected to address the most crucial tasks. The particular provisions are hereby indicated in Appendix A.

This allocation of responsibilities and tasks aims at the materialization of quality maintenance and control, which is further examined in the section below. It is highlighted that all the provisions of the Personnel Guideline are percolated by two main themes which concern personnel training, as well as the hygiene standards that must be observed at all times. In this sense, the guideline demands the training of all employees executing their tasks within the relevant premises, in addition to the special training of workers and employees who are occupied in areas where the potential of contamination constitutes a feasible hazard. In this regard, all the records pertaining to personnel training and respective education must be retained by the respective departments of the manufacturer. Moreover, the GMP Personnel Guideline includes various provisions with respect to detailed hygiene programs, protective garments, and the medical examination of personnel, which are not required to be analyzed in depth for the purposes of this report.

2.2.1. Potential Personnel Gaps

In view of the above, it is evident that a lack of personnel may constitute a bottleneck when it comes to scalability. As per the foregoing section, there are several statutory provisions that require a significant amount of training across all levels of employees and labor workers, let alone the academic and generally educational qualifications pertaining to a particular class thereof. A survey of the WHO among influenza vaccine manufacturers indicates that 80% or more of the companies that participated in the survey stated that they have difficulty in hiring managers in the fields of R&D, production plant, clinical and regulatory affairs and facility

management[24]. Consequently, awareness should be raised with respect to scaling personnel under urgent conditions, such as the COVID – 19 pandemics. An essential part of a manufacturer's capacity to produce a vaccine tackling a global pandemic is inextricably linked to the availability of adequately trained personnel with quite a specific educational profile working in multiple sectors of the manufacturing process. Such necessity for skilled employees in conjunction with the ability to address it may dictate the overall timeline of a vaccine reaching the public.

2.3. Quality Control

One of the EMA's focus areas is quality control, especially when considering the fact that, compared to the FDA, the EMA emphasizes in inspecting the process followed by the manufacturers, whereas the FDA concentrates its inspection efforts towards the final product[25]. In this regard, the Quality Control Guideline[26] provides that each holder of a *manufacturing authorization*[27] must have a Quality Control Department which shall be separate and independent from production. Quality control extends to four (4) main areas which include sampling, vaccine specifications, testing and organization, documentation, and release procedures. These areas ensure that all the necessary and relevant tests are carried out and that materials and products are not released for sale or supply, until their quality is satisfactory, per the determined statutory and scientific standards. To this effect, a finished vaccine product assessment should embrace all relevant factors, including production conditions, results of in-process testing, a review of manufacturing (including packaging) documentation, compliance with Finished Product Specification and examination of the final finished pack.

As hereby indicated, documentation and record tracking are pivotal to the manufacturing process and particularly for the purposes of inspections conducted by the European Medicines Agency. Therefore, applicable documentation must always be readily available to the Quality Control Department such as specifications, procedures, testing report and certificates of analysis and data from environmental monitoring. As far as it concerns sample taking requirements, the samples should be collected and recorded in accordance with approved (by the EMA and the internal departments of the manufacturer) written procedures that describe the method of sampling, the equipment used, the identification of containers sampled, storage conditions, any special precautions to be observed, especially with regard to the sample of sterile or noxious materials and several other factors which are mentioned in detail under Section 6.11 of the *EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use*, *Chapter 6, Quality Control.*

---

[24] *Mapping the Global Vaccine Manufacturing Workforce: Preliminary Results of a Survey among Influenza Vaccine Manufacturers, https://www.who.int/phi/Summary_results_survey_workforce_influenza_vaccines_final.pdf*

[25] Statement is made according to the insights provided by constituents of manufacturing companies operating in the US and the EU and having undergone inspections by both agencies.

[26] The Rules Governing Medicinal Products in the European Union, Volume 4, *EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use*, Chapter 6, Quality Control

[27] To be further discussed in the following sections.

It must be highlighted that the quality control specifications and requirements do not apply exclusively to a pre – inspection stage of setting up a manufacturing facility. Instead, the relevant guideline provides for an Ongoing Stability Programme,[28] by virtue of which, in a post marketing environment, the stability of the vaccine should be monitored according to a continuous appropriate program that will permit the detection of any stability issue. The main purpose thereof is to monitor the medical product over the total of its shelf life.

3. Potential Gaps in the Marketing Authorization Timeline

The table in Appendix B includes a brief and comprehensive description of all the requisite steps pertaining to the issuance of a Marketing Authorization by the European Commission, as such are provided for by the EMA.[29] Evidently, in case the European Medicines Agency intends to exhaust or ends up exhausting the deadlines provided, the overall regulatory process may extend to more than two (2) years. Taking under consideration the catastrophic impacts that the COVID – 19 pandemic has, ranging from health implications to financial losses and the encumbrance of most countries' health systems, the aforementioned timeline is inefficient at best, compared to the emergency use authorizations currently issued by other countries, such as the United States and the United Kingdom. In this regard, several of the processes included in the preceding table can be significantly diminished. To this effect, the EMA puts in a considerable effort in order to closely collaborate with all pharmaceutical and manufacturing companies that aim at producing a vaccine as soon as possible.[30] As a result, the relevant timelines have been significantly shortened, even under circumstances that are not remotely close to the ones experienced during a global pandemic. However, the establishment of a fast – track regulatory mechanism which will respond efficiently to urgent global needs, as the ones that arise during a pandemic, is yet to be executed. In comparison with the licensing efficiency of Operation Warp Speed, the EMA appears to pace itself in terms of the meetings of the ECHMP, which are required in order to assess the marketing authorization applications for the BioNTech – Pfizer[31] and the Moderna[32] vaccines, respectively. Consequently, a severe level of uncertainty is maintained with respect to the potential of reducing the requisite timeline for regulatory approvals under urgent

[28] The Rules Governing Medicinal Products in the European Union, Volume 4, *EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use*, Chapter 6, Quality Control, sections 6.26 et seq.

[29] Obtaining an EU marketing authorization, step - by - step, available at: https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/obtaining-eu-marketing-authorisation-step-step

[30] Statement is made according to the insights provided by constituents of manufacturing companies operating in the US

[31] Update on assessment of the BioNTech and Pfizer BNT162b2 vaccine marketing authorisation application, available at: https://www.ema.europa.eu/en/news/update-assessment-biontech-pfizer-bnt162b2-vaccine-marketing-authorisation-application

[32] Update on assessment of marketing authorisation application for Moderna's mRNA-1273 COVID-19 vaccine, available at: https://www.ema.europa.eu/en/news/update-assessment-marketing-authorisation-application-modernas-mrna-1273-covid-19-vaccine

circumstances. In this respect, the members of the European Union shall be soon called to address the foregoing gap in the operations of the EMA.

4. Manufacturing Authorization

The Manufacturing Authorization, as provided for by *Article 40* of the *EU Directive* under No. *2001/83/EC*, constitutes a separate regulatory approval which is required "*notwithstanding that the medicinal products manufactured are intended for export.*" In contrast with the Marketing Authorization, the Manufacturing Authorization is not linked to particular medicinal products such as a vaccine. Instead, the purpose thereof is the issuance of a regulatory approval regarding the manufacturing facilities of a legal entity within an EU Member – State, regardless of the vaccine that is going to be produced therein. The regulatory procedure by means of which it is determined whether a vaccine may be produced in a specific manufacturing facility is the Marketing Authorization, which, as previously stated hereinabove, regards a specific vaccine but is also extended to the manufacturing process of this particular vaccine. Therefore, the main differences between the Manufacturing and the Marketing Authorization can be summarized as follows:

a) The Manufacturing Authorization is issued by the EU Member – State in which the manufacturing facility is established, whereas the Marketing Authorization is mostly issued on a European – central level.
b) The Manufacturing Authorization is issued with respect to a manufacturing facility, while the Marketing Authorization is issued with respect to a particular product. The intersection point of the two is the inspection by the EMA of the facilities in which a vaccine is produced. Should these facilities be established in the European Union, they must have received a Manufacturing Authorization by the competent authorities of the respective Member – State.

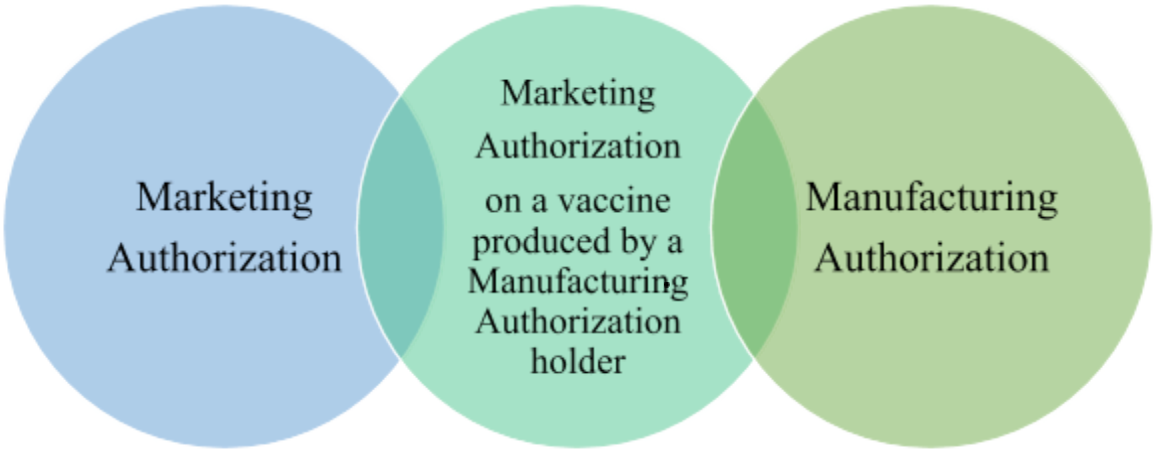


Figure 4. Manufacturing & Marketing Authorization

The extent of the Manufacturing Authorization reached both total and partial manufacturing, whereas the processes it covers also include dividing up, packaging and presentation of the final medicinal product.

1. Introduction to the FDA Regulatory Framework on Vaccine Manufacturing

The US Food and Drug Administration (FDA) serves a similar function compared to EMA as the regulatory body responsible for approval of drug products in the US. The procedures required by both agencies are similar generally, although the overall documentary requirement and duration of FDA approval is understood to be a bit more stringent than its European counterpart.[33] This is colored by the fact however, that new COVID-19 vaccines are being developed and approved in record breaking time by the FDA, hence the conventional differences between these two agencies may not apply for this case.

Additionally, new COVID-19 vaccines will likely be approved under the Emergency Use Approval (EUA) scheme, which further expedites the process, the extent of which will be discussed in further detail below. This section will include a brief overview of the EUA approval procedure, some important concepts used in the approval process, and relevant technical documents.

2. Overview of FDA Emergency Use Approval

On January 31st, 2020, the US Department of Health & Human Services (HHS) issued a declaration under Section 319 of the Public Health Service Act that a public health emergency exists as a result of confirmed cases of 2019 Novel Coronavirus (2019-nCov). On the basis of such determination, on March 27, 2020, the Secretary of HHS then declared that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic, pursuant to section 564(b)(1) of the Federal Food, Drugs, and Cosmetics Act, which identifies four criteria that must be determined by the FDA:[34]

- The chemical, biological, radiological, or nuclear (CBRN) agent referred to in the March 27, 2020 EUA declaration by the Secretary of HHS (SARS-CoV-2) can cause a serious or life-threatening disease or condition.
- Based on the totality of scientific evidence available, including data from adequate and well-controlled trials, if available, it is reasonable to believe that the product may be effective to prevent, diagnose, or treat such serious or life-threatening disease or condition that can be caused by SARS-CoV-2.

[33] Kashoki M, et al. A Comparison of EMA and FDA decisions for new drug marketing applications 2014-2016, 2020, Clin Pharmacol Ther, 107(1), at 195 to 202.
[34] 21 U.S.C. 360bbb-3(b)(1)

- The known and potential benefits of the product, when used to diagnose, prevent, or treat the identified serious or life-threatening disease or condition, outweigh the known and potential risks of the product.
- There is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating the disease or condition.

A fill-finish facility, as part of the manufacturing chain of the drug product, will be required to provide documentation in support of the above criteria. FDA issued the following recommendation regarding manufacturers in an EUA application for COVID-19 related drug products:

> "Sufficient data should be submitted to support drug substance (DS) and drug product (DP) manufacturing to ensure the quality and consistency of the vaccine product that is produced. FDA generally expects a minimum of three Process Performance Qualification (PPQ) lots per manufacturing facility to support the consistency of vaccine quality. In addition, critical process parameters and in-process controls of specific unit operations should be qualified/validated. Evidence should be provided that all DS and DP manufacturing sites, including testing sites, are adequately qualified/validated to ensure that the equipment/process meets all predetermined specifications/intended purposes, and the production process is controlled and operates with quality oversight consistent with CGMP requirements. If more than one manufacturing facility is used to produce DS and DP, data should be provided to support the consistency of vaccine quality between manufacturing sites."[35]

Fill-finish manufacturing (or aseptic processing) is an important step in the manufacturing process and contributes a significant amount of risk to the entire manufacturing process, thus it is important to identify and document how each source of risk can be monitored and controlled.[36] The "Process Performance Qualification" procedure is emphasized in the above paragraph as it is a central component to the approval process of a manufacturing facility. This procedure is nested in a larger concept of "Process Validation", which will be discussed in further detail below.

3. Process Validation

An important concept specifically for drug manufacturers involved in the FDA approval process is "Process Validation", which relates to the commercial manufacturing process specifically.[37] Process validation is evaluated in three separate stages, the sections below will provide a brief summary of each:

[35] Emergency Use Authorization for Vaccines to Prevent COVID-19, Oct. 2020, Center for Biologics Evaluation and Research. Available at: https://www.fda.gov/media/142749/download
[36] See Section I for a detailed discussion on the fill-finish manufacturing process
[37] Process Validation: General Principles and Practices, Jan. 2011, Center for Biologics Evaluation and Research. Available at: https://www.fda.gov/media/71021/download

Process design. The activity of defining the commercial manufacturing process that will be reflected in planned master production and control records. The goal of this stage is to design a process suitable for routine commercial manufacturing that can consistently deliver a product that meets its quality attributes.[38]

This design process is often conducted in coordination with the drug product design itself, and therefore each drug product may come with a prescribed manufacturing process that is being approved along with the final product. Hence products that utilize older technologies will often be able to take advantage of known and tested manufacturing processes.

This is true for fill-finish manufacturing as well. For example, adenovirus-based vaccines have been in production for numerous decades for multiple different vaccine constructions, hence the factors and variables of production are well known. On the other hand, mRNA-based vaccines have just been developed by Pfizer and Moderna will likely come with additional requirements that may create new risk factors.

Process Qualification. The process qualification stage contains two elements: design of the facility and qualification of the equipment and utilities, and process performance qualification (PPQ).[39] The first stage must be conducted because it is not enough to simply rely on the provided operating parameters of purchased equipment and utilities. Each component of the fill-finish process must first be tested for reliability before the appropriate risk factors can be identified and the entire process validated.

Typically for fill-finish processing, the (PPQ) test will take the form of a process simulation (widely known as the "Media Fill" process), where a nutrient medium is filled into vials, which are then incubated to detect potential microbial contamination. All other parameters should be set to reflect the commercial production cycle, such as the size, quantity, and duration of the batch. All expected human manipulations should also be included, even if not necessary for that particular batch in order to simulate a "worst case scenario".

The FDA guidance recommends at least three consecutive separate successful runs during the initial line qualification.[40] A written protocol that specifies the manufacturing conditions, controls, testing, and expected outcomes is essential for this stage of process validation.[41]

Continued Process Verification. The goal of the third validation stage is continual assurance that the process remains in a state of control (the validated state) during commercial manufacture.[42] An ongoing program to collect and analyze product and process data that relate to product quality must be established. Documentation from this

[38] Id. at 8.
[39] Id. at 10.
[40] Emergency Use Authorization for Vaccines to Prevent COVID-19, at 7.
[41] Process Validation: General Principles and Practices, at 12.
[42] Id. at 14.

program will also be essential for the continued monitoring by FDA during commercial manufacturing.

4. Comment

As shown in the sections above, obtaining FDA approval is a long and complex process, even though drug manufacturers such as fill-finish facilities only come in the picture post clinical trials and after the NDA have been submitted. There are two major regulatory hurdles: firstly, the product-focused nature of the FDA requires that drug manufacturers be approved for each drug that they produce. This naturally creates the situation where facilities with a longer history and relationship coordinating with the FDA will have an advantage over newer facilities. Secondly, the "media fill" process required by the FDA is especially time consuming. As separate PPQ batches must be prepared and incubated for testing. If any errors are detected and adjustments required, the entire process must be repeated again. This will easily add significant delays to preparing the documentation required for an NDA.

IV. Regional Differences in Vaccine Production

In addition to the regulatory differences between FDA and EMA approval regimes, vaccine production also varies regionally. This is true especially for the different standards that apply to the glass vials used in the fill and finish manufacturing process.

According to European and American standards, glass vials used for vaccines shall be "neutral" borosilicate glass（5.4 borosilicate glass vials). However, China uses "low" borosilicate glass (3.3 borosilicate glass), and soda-lime glass and India uses soda-lime glass (7.8 expansion soda-lime glass amber) as glass vials in vaccines.

There are four types of glass used in the bottles and vials, the borosilicate glass has the most stringent extractable standard than soda lime glass. Also, "neutral" borosilicate glass has stronger tolerance and resistance.

Information on the types of glass used in the bottles and vials.

Type I Glass – Containers made of Type I Borosilicate glass are generally used for preparations that are intended for parenteral administration. Highly resistant borosilicate glass.
Type I Borosilicate Glass has the most stringent extractable standard. Our glass vials are borosilicate glass.

Type II Glass – Treated soda lime glass.
Type II Treated Soda Lime Glass Formula (Type 3) has been treated in the annealing oven (lehr) with sulfur to reduce alkali solubility. This treatment produces a very slight tinted appearance.
Type III Glass – Soda lime glass.
Type III Soda Lime Glass has been tested and shown to have a specified extractive level. Soda glasses not meeting Type III qualification are classified as USP type NP. Our bottles and jars are Type III Soda Lime Glass.
Type NP Glass – General purpose soda lime glass.

Glass vials used in vaccines are required to be resistant to low temperatures and can endure turbulence and are able to be transported all over the world. Its production requires high technology support and is very time consuming.

Standard	3.3 Expansion Borosilicate Glass	4.9 Expansion Borosilicate Glass (Clear)	5.4 Expansion Borosilicate Glass (Amber)	7.8 Expansion Soda-Lime Glass (Amber)	9.1 Expansion Soda-Lime Glass (Clear)
ASTM E-438	Type 1 Class A	Type 1 Class B	Type 1 Class B	Type 2	Type 2
US Pharmacopoeia (USP)	Type 1	Type 1	Type 1	Type 3	Type 3
European Pharmacopoeia (EP)	Type 1	Type 1	Type 1	Type 3	Type 3

The glass vial should have good ‘water tolerance’: The stronger the water tolerance, the less risks there are in reacting with drugs and so the better quality the glass bottles are. According to different water tolerance from a lower value to a higher value, pharmaceutical glass can be divided into soda-lime glass, low borosilicate glass and neutral borosilicate glass. Details refer to the table below.

According to data, though the major component of neutral borosilicate glass is the ordinary quartz sand (silica), its manufacturing process is not ordinary. The boron content in neutral borosilicate glass is greater than 10% and the alumina content is close to 7% and such characteristics lead to such problems as too high viscosity, higher melting temperature, etc. during melting. Meanwhile, requirements for bubble contents, chemical uniformity and temperature uniformity in neutral borosilicate glass are much higher than that in ordinary glass.

Chemical Components (Mass Fraction/%) And Property	Glass Classification		
	Borosilicate Glass		Soda-Lime Glass
	3.3 Borosilicate Glass	Neutral Glass 1	

B2O3	12-13	8-12	
SiO2	About 81	About 75	70-75
Na2O+K2O	About 4	4-8	12-16
MgO+CaO+BaO + (SrO)	--	About 5	10-15
Al2O3	2-3	2-7	0.5-2.5
Average Coefficient ofLinear Expansion (20-3000C) X10-6/K-1	3.2-3.4	4-5	8-10
Water Resistance by Particle Method	Strong	Strong	Weak
Acid Resistance	Strong	Strong	Medium
Alkaline Resistance	Medium	Medium	Weak
Processability	Poorer	Good	Good
Mechanical Strength	Good	Good	Poor

Though all of them are glass, there are significant differences among them. Glass itself is not so inert and when drugs contact with glass for a long time, the alkali metal ions will be precipitated and arsenic, antimony, and aluminum ions will leak into the drug solution among which arsenic ions and antimony ions are toxic heavy ions and aluminum ions are the important risk factor for Alzheimer's disease. And vaccines are not ordinary liquids but are filled in glass bottles following several basic requirements, e.g., clean and sanitary, resistant to low temperatures, anti-wear, good air tightness, no chemical reactions. Among them, no chemical reactions are the most important requirement. Vaccines are chemical agents which once reacting with glass bottles will be polluted and lead to safety hazards.

Because of the high technological threshold, neutral borosilicate glass has long been monopolized by three large enterprises i.e., SCHOTT AG in Germany, Nipro Pharma Corporation in Japan and Corning Incorporated in American. In capacity, as the global largest glass vial manufacturer and pharmaceutical packaging supplier, SCHOTT AG declared that the company aims to deliver 2 billion doses of COVID-19 vaccine. Nipro plans to deliver in excess of 1 billion doses. Corning plans to produce an extra 164 million vials annually by the end of 2021. The glass vials companies multiply their production ability more than pre-pandemic.

However, due to the epidemic's severe spreading over the world, the demand for neutral borosilicate glass vials surges and causes shortage. According to the Wall street journal: global scarcity of glass supply has appeared. Even vaccines for COVID-19 are developed, they cannot be transported all over the world timely and efficiently. In the country without ability to produce a large amount of neutral borosilicate glass vials will have shortage in the glass vials due to inefficiency transportation and higher market price.

Shortage of vaccine vials means that even if the vaccines for COVID-19 are developed successfully, there are still billions of people all over the world who could not be vaccinated. The vaccine development is hard to be kept up with by glass vials production, especially with two doses of injections.

Currently, China has four COVID vaccines in III phase. Two are from Sinopharm; one is from Sinovac Biotech; one is from CanSino Biologics). The Development Center for medical Science & Technology National Health Commission predicts that there are 610 million doses produced in 2020 and 1 billion doses produced in 2021.

Every year, China demands 80 billion doses of glass vials, including 40 billion doses of ampule bottles,15 billion doses of molded bottles and 15 billion doses of control bottles. As the largest producer of glasses, Shandong Pharmaceutical Glass Co produces 1.2 billion doses of ampule bottles, 7 billion doses of molded bottles and 1.2-1.4 billion of control bottles. There are several large suppliers of glass vials in China as well and looks could satisfy the extra demand of glass vials caused by COVID vaccine. However, there is only 7% - 8% of glass vials made of neutral borosilicate glass in China. The rest of them are either made by low borosilicate glass or soda-lime glass. The standard of China for glass vials used in vaccines is “low” borosilicate glass (3.3 borosilicate glass) and soda-lime glass, so there is no motivation for vaccine producers to choose “neutral” borosilicate glass with higher price.

However, China claims there is no shortage in the glass vials. In 2017, the National Medical Products Administration suggested not to use low borosilicate glass (3.3 borosilicate glass) and soda-lime glass, but there are no mandatory requirements.

Similarly, in India, there is no shortage in the glass vials since India uses soda-lime glass. India’s Bureau of Standard categorizes soda-lime-silica glass that has been specially treated on its internal surface as ‘Type 1’ medical grade, and suggests that the chemical resistance of the internal surface of containers made from soda-lime-silica glass improved by a treatment during production to produce a chemical resistance equal to that of those made from borosilicate glass for single use.

V. The Limitations of Cold Storage

A special requirement of sterile drug products such as vaccines that covers every stage of its manufacturing process is that the product must be constantly stored at low temperatures. This ranges from -20 degrees Celsius that commercial freezers can achieve, to ultra-low temperatures that require special equipment. This applies to fill and finish manufacturing as well, since all filled vials must be stored at the designated temperature before they can be shipped for distribution. Any increase in manufacturing capacity must also be accompanied by a corresponding expansion in storage capacity. In a time when cold storage will likely be in high demand, this will be significantly more difficult to accomplish.

Storage at Fill & Finish Facilities

The following diagram depicts the cold chain. The term cold chain refers to the temperature-controlled environment for vaccine production, storage, and distribution. Throughout the cold chain, some vaccines need to be kept at extremely cold temperatures to

maintain efficacy. This poses a problem not only for shipping, but for storage at manufacturing facilities, regional distribution centers, and local points of care. Developed countries have begun to expand their cold storage capacity in preparation for COVID-19 vaccines, but there are many underdeveloped countries where the storage and distribution of a COVID-19 vaccine will be difficult if not impossible given limited cold chain capacity. The news media has focused its attention on the distribution of vaccines, logistical challenges, and the temperature requirements of various leading candidates, but storage at manufacturing facilities is also essential for the roll-out of a vaccine. Fill and finish facilities--the first step in the cold chain--will require refrigerators and freezers just as the regional distribution centers and local points of care do.

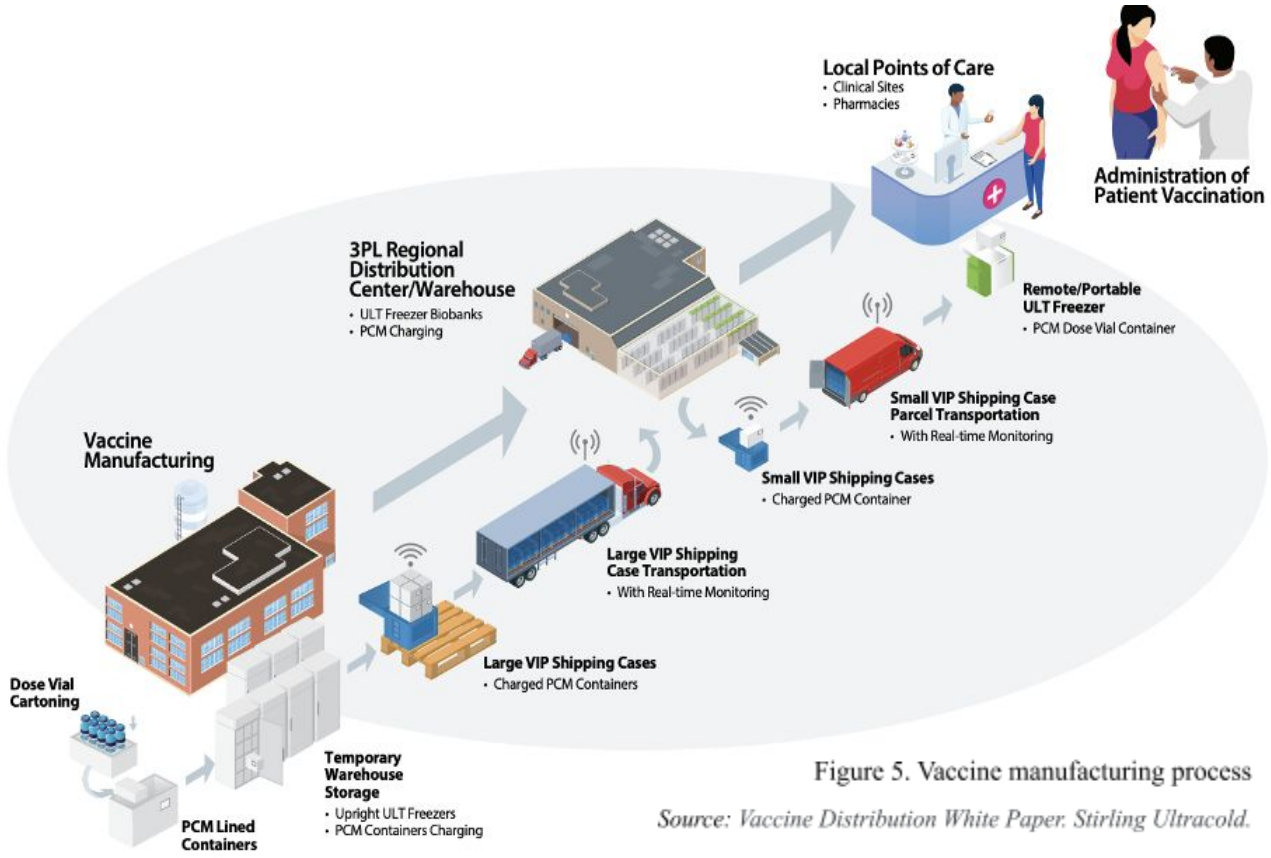


Figure 5. Vaccine manufacturing process

Source: Vaccine Distribution White Paper. Stirling Ultracold.

Supply Chain Gap/Bottleneck

Cold storage at manufacturing facilities may be a bottleneck given the unprecedented scale of production of a COVID-19 vaccine. The number of vials a firm can process is limited to the extent it can store those vials before shipping. Therefore, a shortage of cold chain storage can slow down vaccine production. Do manufacturing firms need to build freezer farms to handle this scale of vaccine production as UPS is doing at its distribution center in Louisville,

Kentucky.[43] The UPS freezer farm is a warehouse filled with seventy upright freezers which are capable of holding 48,000 vials each.

Scalable production of a vaccine will likely require additional cold storage capacity at manufacturing plants. Few vaccine manufacturers are ready to store vaccines at temperatures as low as -80 degrees Celsius,[44] as Pfizer/BioNTech's mRNA vaccine requires. While Moderna's mRNA vaccine can be stored in a typical freezer at -20 degrees Celsius, Pfizer/BioNTech's vaccine requires special freezers capable of reaching ultracold temperatures. These freezers, known as ultra-low temperature (ULT) freezers, are capable of reaching temperatures as low as -86 degrees Celsius.

Much of the news media has rightly focused its attention on the temperature requirements of Pfizer/BioNTech's and Moderna's mRNA vaccines because the pharmaceutical supply chain is currently not equipped to handle these vaccines. The prevalent temperature capabilities of the pharmaceutical supply chain are between 2 and 8 degrees Celsius.[45] Some leading COVID 19 vaccine candidates--such as Johnson and Johnson's or AstraZeneca/Oxford's viral (adenovirus) vaccines--do not require the ultracold temperature control, however the question needs to be asked whether the 2-8 degrees Celsius units common in the pharmaceutical supply chain are available for storing a COVID 19 vaccine or occupied with other vaccines. Will production capacity (including cold storage units) shift from being used for other vaccines to COVID-19 vaccines?

Obstacles to Cold Storage Capacity

There are three potential obstacles to expanding cold storage capacity at fill and finish manufacturing plants. The first is that the contract manufacturers will not have the space to install additional freezers. One industry expert explained that their production capacity was limited by the quantity of glass vials that could be stored in their warehouses. The second obstacle has to do with investment incentives: do firms have the incentive to invest in cold storage units and/or facility expansion? Firms may not want to invest in facility expansion if they think that the immense scale of production required by the pandemic is only temporary. That may be the case if vaccination against COVID-19 is not needed again in the future. The third potential obstacle is that the high demand for pharmaceutical-grade freezers cannot be met by suppliers in a short timeframe given their production capacity.

How can investment risk be mitigated? Stirling Ultracold, a ULT freezer manufacturer headquartered in the USA, recommends buying their ULT freezers as a way of reducing risk because their freezers have a larger temperature range (-86 to -20 degrees Celsius) than the conventional ULT freezer (-86 to -50 degrees Celsius). The conventional ULT freezers will be

[43] Gellees, David. How to Ship a Vaccine at - 80 Degrees Celsius. Sept. 18, 2020. https://www.nytimes.com/2020/09/18/business/coronavirus-covid-vaccine-cold-frozen-logistics.html
[44] Vaccine Distribution White Paper. *Stirling Ultracold.*
[45] DHL White Paper. *Delivering Pandemic Resilience.* September 2020.

capable of storing the Pfizer/BioNTech vaccine but not the Moderna vaccine, nor the Johnson and Johnson or Astrazeneca/Oxford vaccine. Thus, investing in a conventional ULT freezer carries more risk than investing in the Stirling Ultracold freezer because the latter is capable of meeting the requirements of a greater number of vaccines. For example, the Stirling Ultracold ULT is capable of storing either of the mRNA vaccines.

Further Research

This section provided an overview of vaccine temperature requirements. In order to scale cold storage capacity, however, a number of questions need to be answered. Who are the lead manufacturers of pharmaceutical-grade freezers? Where are these manufacturers located? What production constraints do these manufacturers face? Are these manufacturers capable of mass-producing their product? Are they willing to expand production capacity? If so, what is the timeline? What is the (extended) lead time for delivery of their product? What is the cold storage capacity of manufacturing facilities? What are the regulations on the production and use of cold storage units for vaccines?

VI. Conclusion

This report aimed to illuminate the "black box" of the fill and finish manufacturing process, the cog in the supply chain fraught with proprietary knowledge and heavily reliant on technical expertise. This unbiased assessment highlighted the issues with scalability of a COVID-19 vaccine, a realistic view on timelines, but also provided insights into the dangers of rushing a vaccine for emergency use. Although our report did not provide all of the answers for this complicated process, our goal was to better inform the public through thoughtful analysis. The media only provides a small glimpse into this complex world and can sometimes glamorize one aspect of the vaccine development process while diminishing another.

Human expertise as well as specialized equipment and regulations are critical to vaccine development and cannot be forgotten, even as the first batches of the Moderna and Pfizer vaccines are currently being administered to the public. While we celebrate the good news, we also caution the public that the scalability to continue to inoculate the public remains a concern, and the lessons learned from this pandemic must be captured in order to launch a more appropriate response in the future.

VII. Appendix

Appendix A: Roles and Responsibilities

Some of the most significant responsibilities of the Head of Production are the following:

a. To ensure that products are produced and stored according to the appropriate documentation.
b. To approve the instructions relating to production operations and to ensure their strict implementation.
c. To ensure the required initial and continuing training of his department personnel.

In a similar rationale, some of the responsibilities of the Head of Quality Control include the following:

a. To approve or reject, as he or she sees fit, starting materials, packaging materials, intermediate, bulk and finished products.
b. To ensure that all necessary testing is carried out.
c. To approve specifications, sampling instructions, test methods and other Quality Control procedures.

Apart from the individual responsibilities of each particular department, the Head of Production, Head of Quality Control and the Head of Quality Assurance or Quality Unit, provided that the latter is required in a manufacturing facility, share several joint responsibilities, which extend to the following sectors:

a) The authorization of written procedures and other documents, including amendments.
b) The monitoring and control of the manufacturing environment.
c) Plant hygiene.
d) Process validation.
e) Training.
f) The approval and monitoring of suppliers of materials.
g) The approval and monitoring of contract manufacturers and providers of other GMP related outsourced activities.
h) The designation and monitoring of storage conditions for materials and products.
i) The retention of records.
j) The monitoring of compliance with the requirements of Good Manufacturing Practice.
k) The inspection, investigation, and taking of samples, in order to monitor factors which may affect product quality.
l) Participation in management reviews of process performance, product quality and of the quality management system and advocating continual improvement.
m) Ensuring that a timely and effective communication and escalation process exists to raise quality issues to the appropriate levels of management.

Appendix B: EMA Approval Timeline

No.	Step	Details	Timeline
1.	**Submission of Eligibility Request**	The applicant submits an eligibility request in order to verify that the product can be evaluated under the centralized procedure.	T – 7 to 18 months
2.	**Notification of intention to submit an application**	The applicant notifies the EMA on its intention to submit an application for a Marketing Authorization	T – 7 months
3.	**Appointment of Rapporteurs**	The rapporteurs conduct the scientific assessment and are appointed by the Committee for Medicinal Products for Human Use (CHMP)	T – 7 months
4.	**Pre – Submission Meetings**	Pre-submission meetings constitute the best opportunity for applicants to obtain procedural and regulatory advice from the EMA. They are conducted prior to the submission of the Marketing Authorization application. Their use is to speed up the whole process.	T – 6 to 7 months
5.	**Reconfirmation of the Submission Date**	The applicant reconfirms the date on which the Marketing Authorization will be submitted	T – 2 to 3 months
6.	**Submission of Application**	The applicant submits the Marketing Authorization	T
7.	**Validation of Application**	The EMA performs a technical validation of the application it receives. The objective is to make sure all essential regulatory elements required for scientific assessment are included in the application prior to the start of the procedure.	Not specified. Should the EMA require additional information, it will ask the applicant to supply this by a deadline.
8.	**Scientific Evaluation**	Conducted by the CHMP, the latter acquires input from the Pharmacovigilance Risk Assessment Committee (PRAC) on aspects regarding a risk – management plan and the Committee for Advanced Therapies (CAT), if the role of the latter is deemed necessary.	T + 210 active days
9.	**CHMP Scientific Opinion**	The EMA published the CHMP scientific opinion.	Following the completion of the scientific evaluation.
10.	**European's Commission Decision on Marketing Authorization**	The EU Commission makes a legally binding decision based on the EMA's recommendation.	67 days upon step No. 9.

Appendix C: FDA CGMP Overview

Sterile Drug Products Produced by Aseptic Processing - A Summary of Current Good Manufacturing Practices

The regulatory framework regarding the manufacturing of sterile drug products using aseptic processing is provided by the Code of Federal Regulations (CFR) parts 210 and 211, which address current good manufacturing practice for drugs. FDA has also published two corresponding guidance for industry documents: *Sterile Drug Products Produced by Aseptic Processing - Current Good Manufacturing Practice* (CGMP), and *Guideline for the Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products* (Submission Guidance). These two documents provide detailed procedures to be taken by aseptic manufacturing facilities, and the relevant documentation that is required by FDA. The sections below will provide a very brief overview of the content of these two documents.

Buildings and Facilities. The aseptic processing facility should have multiple separate and defined areas of operation that are controlled for microbial activity depending on the nature of the operation. The most important locations to note are the critical area and the supporting clean areas associated with it.
A critical area is one in which the sterilized drug product, containers, and closures are exposed to environmental conditions that must be designed to maintain product sterility. The critical area should satisfy ISO 5 Designation, however as discussed above, adherence to this standard by itself will not be sufficient. The manufacturer must be able to show that the entire facility is under an appropriate state of control, including any supporting clean areas that are connected to the critical area.

Personnel. Unlike EMA, FDA does not have any concrete requirements for personnel in terms of education or qualification contained in their CGMP. Instead, the primary focus of the guidance document is on personnel training, as it recognizes the paramount importance laboratory and facility personnel play in creating and maintaining an aseptic environment.
Hence manufacturers should have a robust and continuous training and supervision program within the facility with well documented procedures to be followed as part of their record keeping practice.

Components and Containers/Closures. Each component or container that comes in contact with the drug product may potentially become a source of contamination. Hence it is important for the facility to identify each item and create a documented sterilization procedure with established acceptance limits for each item. Any components that fail to meet such defined limits must be rejected.

Process Validation. The FDA defines "process validation" as "the collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product." The goal of this process is to obtain documented data showing that all variables within a manufacturing process are being monitored and controlled, hence it can be scientifically proven that the drug product will be produced within an accepted variance. For an aseptic processing facility, this is done through a process simulation, also known as "media fill", which uses a microbial growth medium in place of the drug product and simulates the entire manufacturing process under a "worst case scenario" in the sense that all potentially envisioned external and personnel manipulations are conducted during the simulation.
The filled containers (final product) are then incubated to detect microbial contamination, and the results are interpreted to access the potential for contamination. This simulation itself is central to the facility validation process as a whole and will be covered in further detail in a separate section.

Laboratory Controls. In aseptic processing, one of the most important laboratory controls is the environmental monitoring program. This program is related to, but independent from the initial establishment of building and equipment standards and should cover all production shifts and include air, floors, walls, and equipment surfaces, including the critical surfaces that come in contact with the product, container, and closures.

This program will become the primary insurance within the aseptic facility that all potential sources of contamination is being actively monitored. The CGMP does not provide any concrete requirements in terms of sampling and frequency of tests, however, these parameters should be carefully selected and designed to ensure a documented and scientifically soundproof that the facility is under the appropriate controls.

Sterility Testing The sterility testing program within a facility is required to be accurate and reproducible. The testing laboratory environment should employ facilities and controls comparable to those used for aseptic filling operations. Only then will the test results provide assurance that any manufacturing deficiencies can be subsequently detected.
The facility should also have a documented procedure for investigating and attributing positive sterility tests. The purpose of this investigation should not only be to identify the source of the contamination, but also to identify the organism found in the sterility test in order to properly attribute the organism to its potential source.

***Process Control Documentation*.** Written documentation of all process and environmental control activities is the primary source of information the FDA will use in order to approve a facility. Hence recording keeping standards is also extensively covered in the CFR.

Appendix D: Methodology

Research began on this topic in the summer of 2020 at the height of the first wave of the COVID-19 pandemic. Students and recent graduates from multiple universities, countries and disciplines completed initial research on vaccine development, the fill and finish process, manufacturing challenges and the availability of critical materials in the vaccine manufacturing process such as glass vials and rubber stoppers. After months of initial comprehensive research, we decided to focus on the fill and finish manufacturing process and the scalability of producing a COVID-19 vaccine capable of reaching the world's population.

In the fall of 2020, the Columbia University capstone research project began with nine student representatives from the School of International and Public Affairs, Columbia Law School and the Mailman School of Public Health. Using the findings from the summer research and guidance from our client, we began to conduct first-person interviews with approximately a dozen individuals with knowledge of the vaccine development process. These first-person interviews were conducted throughout the 12-week semester and included representatives from contract manufacturers, scientists from vaccine development firms, data scientists and pharmaceutical companies across the United States, Europe, China, and India.

Because so little information exists on the fill and finish manufacturing process in the public domain, these interviews proved to be essential to our research and findings. When possible, we attributed specific quotes, diagrams and technical information to specific interviewees and companies; otherwise, we generalized information to provide an overview of a process or issue at hand. All interviews were conducted over video or phone calls spanning 30 minutes to two hours over the 12-week period.

Appendix E: Vaccine Manufacturing - Fill and Finish

The process in which a vaccine is put into an injectable form so that it can be administered to patients is known as fill and finish or simply vaccine manufacturing. In this late-stage of production, the vaccine is sterilized and filled into sterile vials or syringes which hold and protect the product until it is administered to patients. Because the vaccine is administered to healthy patients directly into the bloodstream, bypassing all of the body's natural protective barriers, the companies which specialize in fill and finish must take every precaution to produce a sterile product. The sterility requirement makes vaccine manufacturing a time-consuming and complex process that is not well-understood outside the industry given the proprietary nature of the information. This appendix will describe some of the critical processes involved in vaccine manufacturing in an effort to influence public expectations regarding the time it takes to deliver a vaccine to market.

Aseptic Fill and Finish

There are two approaches to fill and finish: terminal sterilization or aseptic processing. Products which undergo terminal sterilization can withstand heat or irradiation, however vaccines

typically cannot be processed in this way as they are damaged by these methods. Instead, they go through an aseptic process, i.e., aseptic fill and finish. The difference between these processes is that in terminal sterilization the product is sterilized in its final container, whereas in aseptic processing the product is sterilized before it is filled. Terminal sterilization is safer than aseptic processing, as the product is sterilized at the end of the process instead of at the beginning. Aseptic processing carries a greater risk of contamination because the product is exposed after it is sterilized, which is not the case when the product is sterilized in its final container. The sterile product comes in contact with tubing, filling needles, the environment, etc., which are all potential sources of contamination. Therefore, it is preferable from a safety standpoint that "a product is rendered as being sterile as close to the end of a process cycle… as possible. Ideally, this is realized through terminal sterilization…"[46] Almost all product recalls are for products that were aseptically processed. Since terminal sterilization more likely guarantees a sterile product, the FDA mandates that all products which can be terminally sterilized should be.[47]

Glass Vial Processing

Glass vials can be purchased pre-sterilized from suppliers in which case the supplier rather than the contract manufacturer is responsible for washing and depyrogenating the vials. The pre-sterilized vials arrive at the manufacturing facility in aseptic packaging.[48] Further preparation of the vials is not necessary, however unpackaging and transferring them has to be done under extremely high-quality conditions. This poses a contamination risk; for example, debris from the packaging could enter the vials when they are unpackaged. Moreover, there is a risk of supplier error or contamination during shipping. To deal with these risks, fill and finish manufacturing firms may choose to conduct the preparation of glass vials in-house.

The preparation of glass vials in-house first requires washing with Water for Injection (WFI). There are two basic designs of the machines which wash vials: rotary and linear. In a rotary machine, the vials are loaded onto a tray and then taken onto a rotating wheel; whereas in a linear vial washing machine, the vials are loaded onto a tray and then taken onto a conveyor belt which moves in a straight course. Vial washing machines can be further broken down by type in terms of whether a needle or jet is used. To achieve high-throughput, some rotary washers have dozens of needles and some linear washers have hundreds of needles which enter the vials at multiple times throughout the washing process.[49] However, needles can cause chipping of the vials, a problem which water jets alleviate. In some operations, the washing machine is integrated with the fill line, feeding the vials directly into a depyrogenation tunnel which in turn

[46] Wiker, George. Sterile Manufacturing Facilities. *Good Design Practices for GMP Pharmaceutical Facilities. 2017. Pp. 305*
[47] FDA. Sterile Drug Products Produced by Aseptic Process- Good Manufacturing Practice. 2004. Pp. 2.
[48] Agalloco, James and James Akers. Sterile Product Manufacturing. *Pharmaceutical Manufacturing Handbook Production and Processes. Pp. 103*
[49] Erdner, John. Advances in Vial Processing in Pharmaceutical Primary Packaging to Reduce Risk of Vial Damage. https://www.pharmaceuticalprocessingworld.com/advances-in-vial-processing-in-pharmaceutical-primary-packaging-to-reduce-risk-of-vial-damage-and-particle-contamination/

moves them to the filling station. A fully-integrated line allows for a continuous process which minimizes operator intervention.

After the washing cycle, vials are sterilized and depyrogenated by dry heat produced in a batch oven or tunnel sterilizer.[50] Because washing to reduce particles in the first phase of vial preparation can introduce microorganisms which result in pyrogen formation, they require depyrogenation,[51] which consists of the destruction of all endotoxins. Often temperatures of 250 degrees Celsius or higher are utilized for depyrogenation; and these temperatures are enough to accomplish sterilization of the glass vials as well.[52] Some dry heat tunnels may operate at upward of 300 degrees Celsius or higher to increase processing speeds, as the higher the temperature, the less amount of time needed for depyrogenation and sterilization.[53]

Dry Heat Batch Oven	Dry Heat Tunnel
Used in Smaller Facilities	Used in Larger Facilities
Can be used in place of autoclave on heat-stable items that need to be extremely dry: e.g., filling parts, feed hoppers, tools	Cannot be used in place of an autoclave
Equipped with internal HEPA filters	Equipped with internal HEPA filters
Require operator intervention to transfer containers to the filling line	Do not require operator intervention to transfer containers to filling line

Source: Agalloco, James and James Akers. Sterile Product Manufacturing. *Pharmaceutical Manufacturing Handbook Production and Processes.* 2008.

An advantage of a dry-heat tunnel is that it transfers the sterilized and depyrogenated vials directly onto the filling line without requiring operator intervention, whereas the batch oven requires operators to remove the glass vials and manually transfer them to the fill line. In large scale manufacturing, it is common practice for the vial washing machine and depyrogenation tunnel to be fully integrated, where the glass vials are fed directly from the washing machine

[50] Agalloco, James and James Akers. Sterile Product Manufacturing. *Pharmaceutical Manufacturing Handbook Production and Processes.* 2008. *Pp. 103*
[51] Ibid, *Pp. 118.*
[52] Agalloco, James and James Akers. Sterile Product Manufacturing. *Pharmaceutical Manufacturing Handbook Production and Processes.* 2008. *Pp. 118.*
[53] Ibid

onto the conveyor belt of the tunnel.[54] A batch oven, on the other hand, is not integrated with the washing machine or the fill line. Transporting the vials from the oven to the filling line presents a contamination risk. To reduce this risk, batch ovens are sometimes connected to isolators, which create a sealed barrier in which vials are protected from exposure to the environment when transferred to the filling line.

Rubber Stopper Processing

Just as glass vials can either be sterilized and depyrogenated at the fill and finish manufacturing facility or purchased presterilized and ready-to-use, so too can the rubber stoppers be sterilized and depyrogenated in-house or purchased presterilized and ready-to-use. Rubber stoppers that are ready-to-use have been washed, sterilized and lubricated (if lubrication is necessary) by the stopper manufacturer. The stoppers arrive at the facilities in sterile bags and can be transferred directly from the sterile bags onto the filling line.

Given that the drug product is directly exposed to the rubber stopper once it is inserted into the filled vial, it is absolutely essential from an end-user safety standpoint that the rubber does not adversely interact with the drug. Rubber stopper manufacturers, therefore, must use specialized ingredients and processes that ensure that the rubber is pharmaceutical grade or else the stoppers may ruin the drug product it comes in contact with. According to one industry expert, Exxon Mobil once got into the business of manufacturing rubber stoppers. Their rubber stoppers ended up ruining all of the drug products they came in contact with. This situation underscores the importance of establishing close commercial ties with suppliers once it has been confirmed that their stoppers are high-quality and safe to use.

While in-house preparation of glass vials consists of cleaning using Water for Injection (WFI) and sterilization and depyrogenation with tunnel sterilizers or batch ovens, in-house rubber closure preparation consists of depyrogenation by rinsing with copious amounts of hot WFI and sterilization by steam in an autoclave.[55] Though not always applied to the rubber stoppers, silicon can be used as a lubricant to ensure that the rubber stoppers are slippery and move easily during production.[56] Some rubber formulations contain polymer surfaces which do not require silicon for easy maneuverability, but when silicon is applied it must be applied before sterilization.[57] The silicon used in the preparation of rubber stoppers should meet appropriate quality control standards and have no adverse effect on the drug product.[58] Some rubber stopper preparation systems clean, siliconize, and depyrogenate rubber stoppers; examples of manufacturers of these systems include DCI, Gettinge, and Icos.[59] But after being processed in these machines, the rubber

[54] Sterile Product Manufacturing Facilities. *Baseline Pharmaceutical Engineering Guide*. 2011.

[55] Akers, Michael. Overview of Sterile Product Manufacturing. *Sterile Drug Products.* Pp. 187-188
[56] Ibid
[57] Ibid
[58] FDA. Sterile Drugs Produced by Aseptic Processing. Pp. 18.
[59] Akers, Michael. Overview of Sterile Product Manufacturing. *Sterile Drug Products.* Pp. 187-188

stoppers still need to be brought together and sterilized in an autoclave.[60] Then they are sterile transferred to the stoppering process equipment, which inserts the rubber stopper into the neck of the glass vial in a Class 100 critical area. Because the stopper comes in direct contact with the product when it is inserted into the vial, it is essential that it is protected against contamination from the moment it is removed from the autoclave until it is inserted.

Moist Heat Sterilization

Moist heat sterilization is the use of pure steam to destroy microorganisms. Steam sterilizers (autoclaves) and Sterilize-in-Place (SIP) systems are the two main functions which use pure steam. Some facilities are equipped with steam generators to produce the pure steam for these functions.[61] An autoclave is "an apparatus into which moist heat (steam) under pressure is introduced to sterilize or decontaminate materials placed within (e.g., filter assemblies, glassware, etc.)."[62] There are three main phases to an autoclave sterilization cycle: first the air must be removed from the chamber; then steam enters the chamber, increasing pressure and temperature; and finally the sterilizer drain is opened and steam is removed.[63]

An autoclave is used for many different items. They are routinely utilized for "elastomeric closures, process and vent filters, product contact parts, heat stable environmental monitoring equipment, tools and utensils, hoses, sample containers, and other items unaffected by contact with saturated steam at commonly used sterilizing temperature and pressure."[64] Moist heat sterilization is also the most common means of terminal sterilization.[65] Sometimes hot water is sprayed inside the sterilizer instead of pure steam, because pure steam is too hot for some products. The temperature and length of time to which the product is exposed depends on the nature of the product.[66] The autoclave can be used to process "sealed containers of aqueous solutions, suspensions, and other liquids." [67]

Sterilize-in-Place (SIP) is the process of using pure steam to sterilize "large equipment such as mixing tanks, vessel-filter-filler systems, and even complete isolator units." [68] This technique is typically utilized in a closed system, i.e. the interior of the mixing tanks, vessel-filter-filler

---

[60] Ibid
[61] Agalloco, James and James Akers. Sterile Product Manufacturing. *Pharmaceutical Manufacturing Handbook Production and Processes. Pp. 116.*
[62] Sterile Product Manufacturing Facilities. *Baseline Pharmaceutical Engineering Guide*. Pp. 193
[63] Everything about Autoclaves.
https://www.steris.com/healthcare/knowledge-center/sterile-processing/everything-about-autoclaves

[64] Agalloco, James and James Akers. Sterile Product Manufacturing. *Pharmaceutical Manufacturing Handbook Production and Processes. Pp. 117.*
[65] Sterile Product Manufacturing Facilities. *Baseline Pharmaceutical Engineering Guide*. Pp. 53
[66] Importance of Terminal Sterilization in Pharmaceutical Industries
https://www.lfatabletpresses.com/articles/importance-terminal-sterilization-pharmaceutical-industries#:~:text=Terminal%20sterilization%20is%20the%20process,and%20usually%20sterilized%20using%20heat.
[67] Agalloco, James and James Akers. Sterile Product Manufacturing. *Pharmaceutical Manufacturing Handbook Production and Processes. Pp. 117.*
[68] Akers, Michael. Overview of Sterile Product Manufacturing. *Sterile Drug Products (textbook).* Pp. 256

systems or the isolator is sealed off from the surrounding environment.[69] With SIP, the closed system is like an autoclave, capable of withstanding the pressures required for steam sterilization; water or steam sterilizes all inner surfaces.[70] SIP must give close attention to the removal of air and condensate draining after sterilization.[71] Moist heat sterilization is performed with pure steam in an autoclave or SIP system to prepare equipment and materials for exposure to a finished drug product. Materials which cannot be SIP can often be sterilized in a double-door autoclave which leads directly into the Class 100 filling area.[72] The autoclave can be used for a number of items, including closures, filters, and parts, while the SIP is used for mixing tanks as well as vessel-filter-filler systems.

Barrier Technology

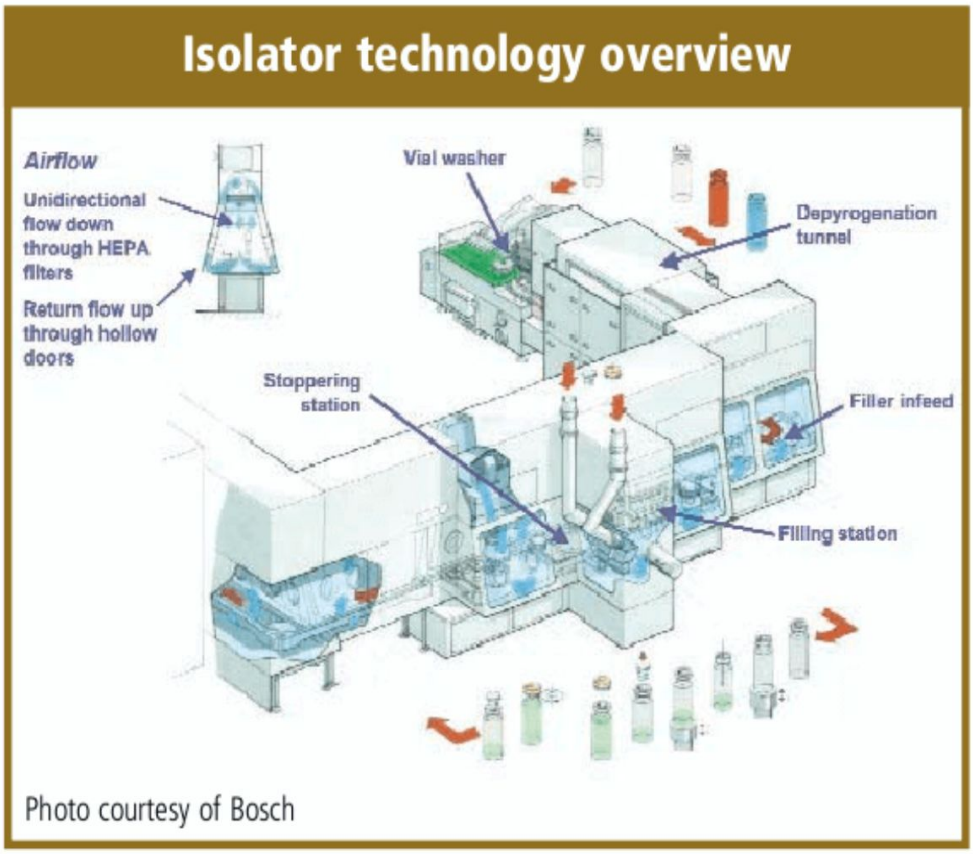
In a traditional cleanroom, the critical area in which the product is exposed to the environment while being filled and stopped is not protected from the surrounding room as it is with more modern designs which use barrier systems. Where barrier systems such as isolators or restricted access barriers (RABS) are used, the risk of contamination is reduced because the critical processing area is closed off from the surrounding environment, and operators do not come in contact with the area. The barrier system creates the primary level of containment, whereas the cleanroom is the secondary level of containment. Designs with only one level of containment, ie. traditional cleanrooms are less reliable than those with two.

The main source of contamination in a cleanroom operation is always the equipment operator, so barrier technologies have been commonly used since the 1990s to reduce operator contact with the critical area and thereby reduce the risk of contamination. A cough, skin flakes or hair are each possible sources of contamination, even though the operators take precautions in the gowns, gloves, and face coverings that they wear. Humans shed five-hundred million skin cells a day! But with the use of isolators, which enclose the filling and stoppering apparatus creating an airtight seal, the operators only have access to the equipment through glove ports. The equipment is designed to ensure that sterile materials such as glass vials and rubber stoppers are transferred into the isolator with minimal exposure to the environment after sterilization. Sterilization tunnels, for example, are often integrated with the isolator, such that glass vials are always protected by HEPA filtered air in the primary level of containment. Batch ovens can also be integrated with an isolator.

The following diagram depicts a fully-integrated fill line using isolator barrier technology. The vial washing machines, the depyrogenation tunnel, the filling and stoppering station are each connected and integrated, creating a continuous process, that is to say, no operator intervention is

[69] Sterile Product Manufacturing Facilities. *Baseline Pharmaceutical Engineering Guide*. Pp. 43
[70] Akers, Michael. Overview of Sterile Product Manufacturing. *Sterile Drug Products (textbook).* Pp. 256
[71] Agalloco, James and James Akers. Sterile Product Manufacturing. *Pharmaceutical Manufacturing Handbook Production and Processes. Pp. 117.*
[72] Agalloco, James and James Akers. Sterile Product Manufacturing. *Pharmaceutical Manufacturing Handbook Production and Processes. Pp.* 125

necessary from the time the vials enter the washing machine until they are stoppered and exit the line. In the upper left-hand corner of the diagram, there is a picture of the airflow inside the isolator. As was already said, the depyrogenation tunnel is supplied with HEPA-filtered air; and so is the inside of the isolator. In this depiction, the HEPA-filtered air is supplied from the top of the isolator and flows in a vertical direction over the filling and stoppering stations. Therefore, the glass vials are protected with HEPA-filtered air throughout the entire continuous process.



Source: Overview of Aseptic Fill/Finish Manufacturing. BioRealty, Inc.
https://www.biorealty.com/blog/overview-of-aseptic-fillfinish-manufacturing/

Further Research

This section provided a detailed description of major operations in the vaccine manufacturing process known as fill and finish. In order to scale production, however, a number of questions need to be answered. Can parts, materials, equipment needed for production be mass-produced? Who are the manufacturers of these parts, materials, equipment? Where are the manufacturers located? What is their current and potential manufacturing capacity? Can their manufacturing capacity be expanded and if so, what is the timeline for such expansion? What are the regulations on the manufacturing of these parts, materials, and equipment?

HVAC System

I. Iso Classifications

The ISO class system is an internationally recognized system for rating the cleanliness of cleanrooms used for conducting aseptic operations. Sterile drug manufacturing facilities are composed of a variety of rooms which are held to different ISO standards.

The area where filling and stoppering operations take place are required to meet ISO 5 classifications, which means that there are less than 3,520 particles of 0.5 microns in size per cubic meter of air. This area is known as the critical zone, where product, product packaging components, and product contact surfaces are directly exposed to the environment. The area immediately adjacent to the critical zone can be qualified as ISO 6 or 7 but depending on the facility the ISO 5 classification is maintained throughout the entire room.[73]

The use of barrier technologies such as isolators and restricted access barriers (RABS) allow for a downgraded surrounding environment; in the case of isolators, it may be acceptable to keep an ISO 8 qualification in the room where it is located, as the isolator creates a seal and completely separates the filling equipment from the environment and personnel.

II. Heating, ventilation, air conditioning (HVAC) system

The HVAC system and its management program are composed of the following basic elements: temperature, relative humidity, air flow volume, air exchange rate, unidirectional air flow, pressure difference relative to adjacent rooms, integrity of HEPA filter, airborne particle count, and micro-bacterial count.[74] A properly designed HVAC system can heat, cool, humidify, dehumidify, supply clean air, dilute contaminants, and create differential pressure.[75]

III. Air

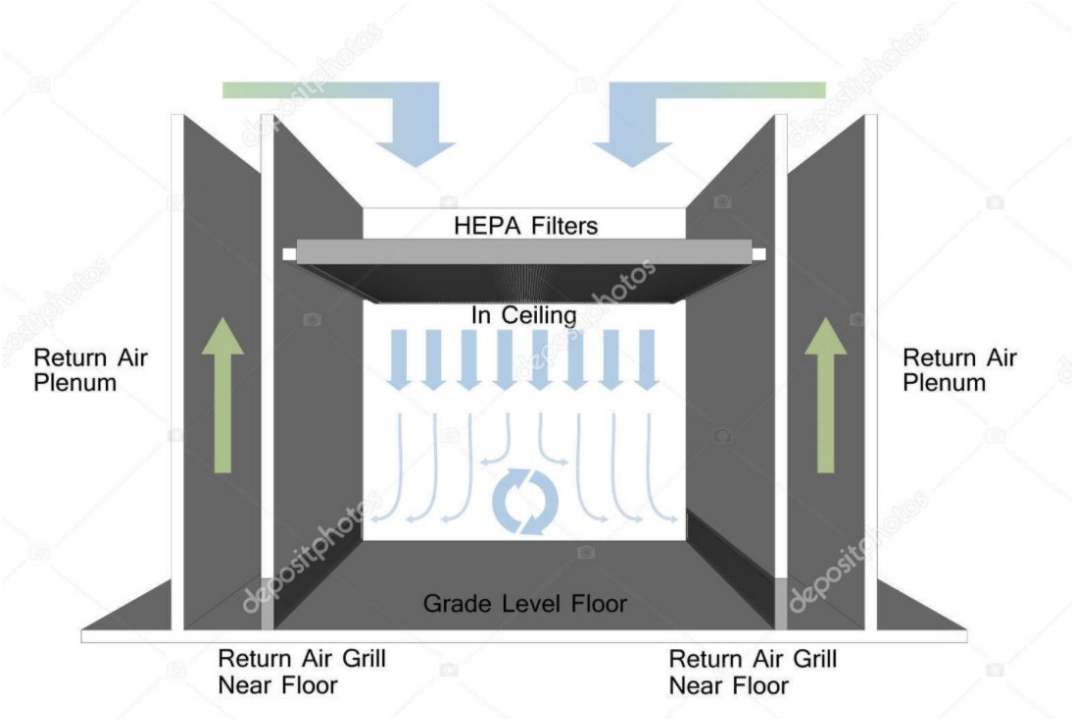
Environmental control of a cleanroom requires close attention to the factors of air filtration, air velocity and airflow. Air filtration is achieved by way of high-efficiency particulate air (HEPA) filters, which remove 99.97% of particles 0.3 microns or larger in size from the air that passes through them. ISO classification standards are met by supplying clean air through HEPA filters. Some configurations employ a double HEPA filtration with the primary filter fitted in the air handling unit and the secondary filter (terminal filter) located within the classified zones.[76]

The velocity of the air supplied by the HVAC system into the clean room has to be sufficient to sweep particles away from the critical zone. The 2004 FDA guidance recommends that the air velocity should be 90 feet per minute (0.45 meters/second), with a range of ±20%, measured at 6

[73] FDA. Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing. 2004
[74] Task Force. *Guidance on the Manufacture of Sterile Pharmaceutical Products by Aseptic Processing.* Can be found at: https://www.pmda.go.jp/files/000153543.pdf
[75] Sterile Product Manufacturing Facilities. Volume 3. *Baseline Pharmaceutical Engineering Guide.* 2011
[76] Ibid

inches below the face of the filter. Other regulatory agencies recommend the measurement to be taken at working height, which is the point just above the vial neck opening.

In addition to controlling the velocity, manufacturing facilities control the direction of airflow. Unidirectional airflow is used to sweep particles away from the critical zone in a roughly parallel singular path. Cleanrooms are designed for unidirectional airflow: air enters the room through HEPA filters installed in the ceiling and exits the room through air returns built into the wall near the floor. The following diagram depicts how clean air circulates throughout the entire room and is re-circulated through the HEPA filters.



Source: https://depositphotos.com/307202508/stock-photo-unidirectional-flow-cleanroom-airflow-design.html

The path of the air is confirmed to be unidirectional by way of smoke studies, also known as visualization studies, which introduce fog at the face of the filter and video record the direction of the fog throughout the room. The interaction of the air with the equipment and personnel can be observed with smoke studies. This method of analysis is used to validate the airflow system upon installation to ensure that it produces unidirectional airflow; and it should be used to monitor the airflow, especially when changes are suspected.

IV. Pressure

Cleanrooms are also pressurized so that air cannot flow into them from less clean areas. The cleaner the room in terms of its classification, the higher the pressure of that room will be relative to the adjacent rooms which are a lower classification. This pressure differential causes air to flow out from the cleaner environment into the less clean environment, not the other way

around. When air flows from cleaner to less clean environments in a sterile manufacturing facility, there is said to be a cascade. The FDA recommends that a positive pressure differential of 10-15 Pascals should be maintained between adjacent rooms of differing classifications with doors closed.[77]

Isolators also utilize pressure differentials to ensure that there is no ingress of contamination; the interior of the isolator is maintained at a higher pressure than the surrounding room so that air can only flow outward, not inward. The reverse is true when dangerous materials are being processed. In order to protect the operator from the dangerous materials in the isolator, a negative pressure differential can be established so that air does not flow out of the isolator.

V. Temperature and Humidity

Temperature and humidity have to be controlled via the HVAC system to produce a comfortable working environment for the operators. Discomfort of the operators due to temperature and humidity can possibly increase the risk of them shedding viable and non-viable particles.[78] These parameters should be adjusted so that the operators do not become too hot in the layers of gowns they are required to wear. Furthermore, temperature and humidity can affect the product; the effect of room temperature on the product temperature, and the effect of relative humidity on product moisture, should be considered.

Fill and Finish Facility Equipment

1. Glass vial washing machine
    a. Rotary
    b. Linear
2. Sterilization tunnel or batch oven
3. Filling station
    a. Peristaltic pump
    b. Piston Pump
    c. Time-pressure mechanism
4. Stoppering station
    a. Sterilized stopper bag
    b. Stopper hopper
    c. Stopper bowl
    d. Stopper linear track
    e. Stoppering device
5. Lyophilizer (freeze-dryer)
6. Crimper
7. Tray loaders
8. Barrier Isolator

[77] FDA. Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing. 2004
[78] Sterile Product Manufacturing Facilities. Volume 3. *Baseline Pharmaceutical Engineering Guide.* 2011

9. Restricted Access Barrier
10. Packaging and labeling equipment
11. Stopper process equipment
    a. Washing
    b. Depyrogenating
    c. Siliconizing
    d. Sterilizing
12. Temperature controls
13. Heating, ventilation, and air conditioning (HVAC) system
14. High-efficiency particulate air (HEPA) filters
15. Mixing tank for formulation/ compounding
16. Stainless steel holding tanks (multi-use)
17. Autoclave
18. Clean-in-place and steam-in-place systems
19. Environmental monitoring devices
    a. Touch plates, swabs, contact plates (Surface monitoring)
    b. Particle detectors
    c. Impaction, centrifugal, membrane samplers (Active air monitoring)
    d. Settling plates (Passive air monitoring)
    e. Anemometer (for measuring air velocity)
20. Sterile filters
21. Filling needles
22. Stainless steel tubing (multi-use technology)
23. Steam generator

Appendix F: FDA Approval Timeline

The following table provides a timeline of a priority FDA New Drug Approval review, this designation means FDA's goal is to take action on an application within 6 months:

No.	Step	Details	Timeline
1	Pre-Submission Activities	The applicant may hold pre-NDA meetings with the Office of New Drug Research (OND). These meetings are held to discuss the content in the application. Historically, the most complete applications have the best outcomes. During pre-NDA meetings, the need for advisory committee meetings is discussed, as well as the risk evaluation mitigation strategy (REMS) and post-marketing surveillance activities. A pre-electronic submission meeting is sometimes held to discuss and/or test the technology (navigation, formatting, and location of datasets).	T-1 to 2 months
2	Application	The applicant submits the New Drug Application.	Day 0
3	Process Submission and Plan for Review	OND receives and processes the application, then begins planning the review. Reviewers from each discipline are assigned to the application, as well as a cross-discipline team leader (CDTL) who oversees the review of the application and identifies areas where there is possible disagreement, say between chemists and clinical reviewers.	Day 0-30
4	Filing/Planning Meetings	The filing meeting ensures that the application is complete and reviewable for each discipline.	Day 30
5	Primary Reviews	Each member of the review team conducts a full review of his or her section of the application. For example, the medical officer and the statistician review clinical data, while a pharmacologist reviews the data from animal studies. Within each technical discipline represented on the team, there is also a supervisory review.	Month 2-6
6	Mid-Cycle Meeting	The review team meets with the applicant for any clarifications and adjustments required during the review process.	Month 3

7	Wrap Up Activities	One of the final steps in the review cycle is the convening of internal labeling discussions, as well as post marketing study requirement/commitment (PMR/PMC) discussions.	Month 5
8	Wrap Up Meeting	A wrap-up meeting is held to discuss any outstanding issues, in-depth labeling, PMRs/PMCs and safety activities.	Month 5
9	Action Date	The OND advisory committee approves the NDA. An action letter is drafted and issued to the applicant.	Month 6

Appendix G: The Manufacturing Process and Supply Chain of a Vial

A COVID-19 Injectable Vaccine

The Manufacturing Process and Supply Chain of a Vial

By Grace Pan, Mira Baum, Yuexin Zhao, and Jerry Canto
Supervised by Professor Jenik Radon

Table of Contents

1. What does it take to make a vial?

The primary goal of this memo is to understand the requirements of vial production processes and to note the potential gaps in the manufacturing of vials. This is the first step to understanding the manufacturing process of an anti-coronavirus injectable vaccine.

What is a pharma vial?

Vials are slim, tall, cylinder shaped glass containers that can be used to contain a wide variety of liquid, specimens, or samples.[79] The main function of a vial is to protect a drug during its shelf life, which includes all steps during manufacturing, transportation, storage, and use.[80]

The anatomy of a vial is described below. Critical attributes related to vial dimensions may include minimum bottom thickness and maximum concavity (the ability to lyophilize, or freeze-dry, efficiently is impacted by these attributes), crown inner diameter (critical to fit with the stopper to ensure container closure integrity, or CCI), crown outer diameter (important to ensure the aluminum seal or flip-off seal that keeps the integrity of the entire system fits together appropriately):[81]

Figure 1: Vial anatomy. Data source: SCHOTT Pharmaceutical Packaging[82]. Image source: Gerresheimer[8]

[79] "Glass Vials | SCHOTT Pharmaceutical Packaging | SCHOTT North America," accessed June 4, 2020, https://www.us.schott.com/pharmaceutical_packaging/english/products/vials.html.
[80] Fran DeGrazio and Lionel Vedrine, "Quality by Design for Primary Container Components," in *Quality by Design for Biopharmaceutical Drug Product Development*, ed. Feroz Jameel et al., AAPS Advances in the Pharmaceutical Sciences Series (New York, NY: Springer, 2015), 365–401, https://doi.org/10.1007/978-1-4939-2316-8_17.
[81] DeGrazio and Vedrine.
[82] "Glass Vials | SCHOTT Pharmaceutical Packaging | SCHOTT North America," accessed June 4, 2020, https://www.us.schott.com/pharmaceutical_packaging/english/products/vials.html.

Finish: The top part of the container, above the neck, shaped to accommodate a specific closure. Includes the collar, the flange, and the crown.
Neck: The portion of the container that is above the shoulder and below the finish. The neck is where the cross-section of the bottle grows smaller to join the finish.
Shoulder: The part of the bottle that joins the wide body and the narrower neck. The slope of the shoulder is one factor in determining how quickly a product will be dispensed when the bottle is inverted.
Body: The main part of the bottle where the sidewalls are usually (but not always) vertical.
Bottom: The entire lower part of the bottle below the sidewalls. The bottom includes the heel, base and pushup. The bottom may have letters and symbols molded into it that indicate the number of the mold cavity that produced the container and the manufacturer. The manufacturer symbol is called a "punt mark". The bottom also may have a small projection that serves as a registration device for labeling and decorating equipment.[83]

What are the materials needed?

Material of the vial

When choosing a vial, the product material is of great importance. How well glass or plastic tolerates an active ingredient depends on its composition. Below is a summary weighing the benefits of glass versus plastic vials:

Table 1: a comparison of the benefits of glass and plastic vials. Source: The Cary Company.[84]

Glass	**Plastic**
Capable of withstanding high temperatures	Smaller temperature range
Will not leach harmful chemicals	Can leach into products
Less permeable	More permeable
Expensive to ship	Easy to ship
Heavy	Light-weight
Dangerous when broken	Kid-friendly
100% recyclable	Not as easy to recycle
High energy to make	Cost-effective to produce

Glass vials are pure, meaning they have no traces of contaminants within their components. Glass is also heat resistant, which is vital because glass vials may be heated to over 500 degrees Celsius. That makes glass vials a common choice for many labs.[85]
There are three common glass types: I, II, and III. Glass type I is borosilicate glass with good chemical resistance and is standard for most pharmaceutical glass vials. It is also preferred when using biologics

[83] "Anatomy of a Bottle," accessed June 4, 2020, https://www.berlinpackaging.com/anatomy-of-a-bottle/.
[84] "Glass vs Plastic: 7 Factors to Consider for Packaging Your Product," *The Cary Company* (blog), February 20, 2019, https://www.thecarycompany.com/about/blog/glass-vs-plastic-packaging.
[85] "How to Select Chromatography Vials," accessed June 12, 2020, http://www.qorpak.com/pages/HowtoSelectChromatographyVials.

(derived from biological methods and primarily composed of sugars, proteins, nucleic acids, and potentially live specimens, as opposed to chemically synthesized). Glass types II and III are soda-silica.[86] The following table describes the differences between these three glass types:

Glass Type	**Composition**	**Use**
Type I	Borosilicate Glass	● borosilicate structure ● good for containing acidic, neutral or alkaline injectable preparations ● resistant to thermal shocks ● can be sterilized prior to or after filling
Type II	Soda-Lime-Silica Glass, with a treatment on the inner surface to increase hydrolytic resistance	● via the special treatment, reaches the same hydrolytic stability as type I glass ● suitable for acidic and neutral injectable preparations ● can be sterilized prior to or after filling
Type III	Soda-Lime-Silica Glass	● average hydrolytic resistance ● good for containing powders and non-aqueous injectables, and can be used for non-parenteral preparations ● must be sterilized by dry heat prior to filling

Table 2: differences between glass types I, II, and III. Data source: from Biomed, "Glass Containers for Pharmaceutical Use." [87]

Plastic vials provide good chemical resistance, lightweight construction, durability and affordability. It is important to note that the type of plastic makes a difference in the vial and its uses. Plastic vials can be made of either polypropylene or poly methyl pentene (PMP).[88] Polypropylene, the material of recyclable containers one might store dinner leftovers in, is the most popular plastic material available. Polypropylene vials have a heat resistance of up to 135 degrees Celsius and are translucent. PMP has a higher heat resistance—up to 175 degrees Celsius—and is transparent, which increases visibility of the sample within the vial.

[86] "Bottles and Vials for Pharmaceuticals," accessed June 5, 2020, https://www.gerresheimer.com/en/products/pharmaceutical-primary-packaging/bottles-vials-made-of-glass.html.
[87] "Glass Containers for Pharmaceutical Use," accessed June 5, 2020, http://www.biomed.co.th/english/Article-USP-Chapter660-EP321-Glass-Containers%20for%20PharmaceuticalUse.php.
[88] "How to Select Chromatography Vials."

Material of the closure

Closures ensure that the contents of vial are secured for storage or transportation, providing a leak-proof, spill-proof barrier. The two most common closures are caps and stoppers. Caps are usually metal or plastic (phenolic, polypropylene, or polyethylene). Phenolic plastic caps are the most temperature tolerant.[89] Polypropylene and polyethylene caps are particularly chemically resistant.[90]

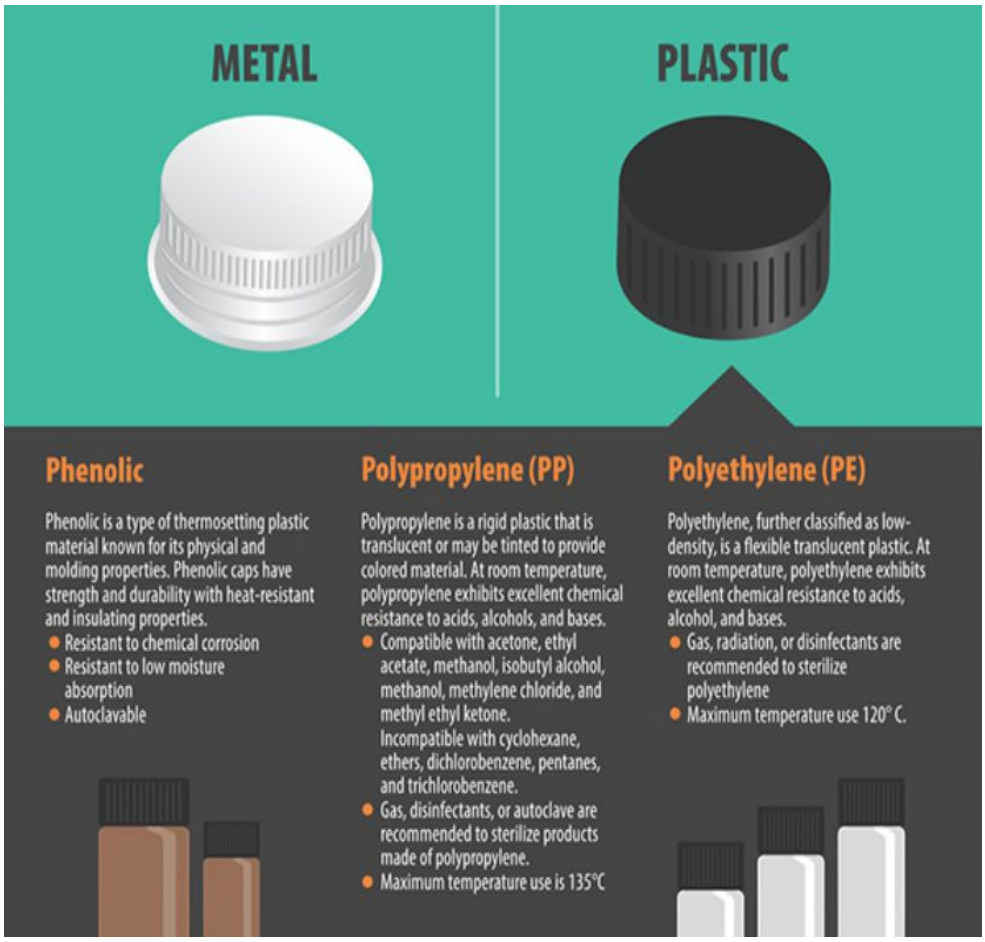


Figure 2: diagram of metal and plastic caps. Source: O.Berk[91]

Rubber stoppers also can be used as a closure for glass vials, but studies have shown there to be quality control issues with natural rubber, due to potential latex allergies.[92] One commonly-used closure style for parenteral liquid or freeze-dried drugs is a glass vial with an elastomeric stopper and an aluminum crimp

[89] "PP-PET-Solid-Liquid.Pdf," accessed June 12, 2020, https://www.gerresheimer.com/uploads/tx_szpdfbook/PP-PET-Solid-Liquid.pdf.
[90] "PP-PET-Solid-Liquid.Pdf."
[91] "PP-PET-Solid-Liquid.Pdf."
[92] M. N. Primeau, N. F. Adkinson, and R. G. Hamilton, "Natural Rubber Pharmaceutical Vial Closures Release Latex Allergens That Produce Skin Reactions," *The Journal of Allergy and Clinical Immunology* 107, no. 6 (June 2001): 958–62, https://doi.org/10.1067/mai.2001.115630.

cap.[93] For parenteral drugs, rubber stoppers are preferred because one does not need to remove the stopper, and can pierce it with a needle, thus reducing risk of contamination. Rubber stoppers can be treated with fluorocarbon film to prevent stoppers from sticking, and to prevent clumping between drug and closure. It is unclear whether or not this is for lyophilized drugs only.[94]

There are a few types of rubber.[95] Synthetic rubbers are used almost exclusively due to allergen issues with natural rubbers. Halobutyl rubbers, and in particular, bromobutyl and chlorobutyl rubber, are most common. Butyl rubbers require thermal cracking of natural gas or lighter crude oils. ExxonMobil Chemical is one of the major manufacturers of butyl rubber.[96] Different styles of stoppers are needed for serum vs. lyophilized drugs. See figure and table below.[97]

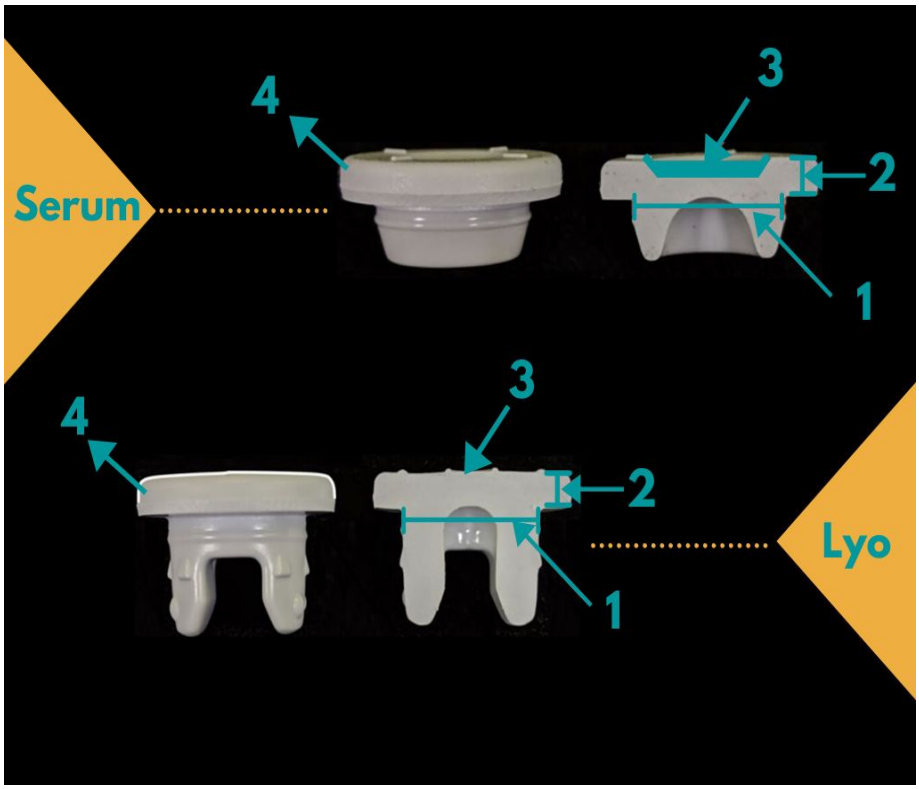


Figure 3: diagrams of serum vs. lyophilization stoppers. See table below for explanation. Photo and data source: Ovadia et al.

[93] Roman Mathaes et al., "The Pharmaceutical Vial Capping Process: Container Closure Systems, Capping Equipment, Regulatory Framework, and Seal Quality Tests," *European Journal of Pharmaceutics and Biopharmaceutics: Official Journal of Arbeitsgemeinschaft Fur Pharmazeutische Verfahrenstechnik e.V* 99 (February 2016): 54–64, https://doi.org/10.1016/j.ejpb.2015.11.016.
[94] "Stoppers - West Pharma," accessed June 12, 2020, https://www.westpharma.com/products/vial-containment-solutions/stoppers.
[95] "Stoppers - West Pharma."
[96] "Butyl Rubber | Chemical Compound," Encyclopedia Britannica, accessed June 12, 2020, https://www.britannica.com/science/butyl-rubber.
[97] Robert Ovadia et al., "Quantifying the Vial-Capping Process: Reexamination Using Micro-Computed Tomography," *PDA Journal of Pharmaceutical Science and Technology* 74, no. 2 (March 1, 2020): 171–84, https://doi.org/10.5731/pdajpst.2019.010363.

	#	Serum	Lyophilization	Impact on CCI?
Key similarity	1	Outer diameter of the plug is the same for both		Major
Key differences	2	Flange slightly thicker than lyo stopper	Flange slightly thinner than serum stopper	Minor
	3	Dimpled top	Flat top	Minor
	4	No film on top	Film on top	Minor
	N.P.	Concavity and minimal structural support	Vent and legs to provide structure.	Major

Table 3: Explanatory table for Figure 3. Identifies similarities and differences between serum and lyophilization stoppers. N.P. indicates an aspect not pictured in Figure 3. Data source: Ovadia et al.

What are the specs of the vial?

Size. Considerations to keep in mind when sizing the vial include overall diameter (OD), length, wall weight, and fill capacity. These specifications will depend on the nature of the API (i.e., whether it is liquid, powder, frozen, etc.)

Neck finish styles. Five common neck finish styles include: shell vial, flat crimp, tapered crimp, snap neck, and screw neck. Flat crimp and tapered crimp neck finishes are commonly used for lyophilized and serum vials.[98]

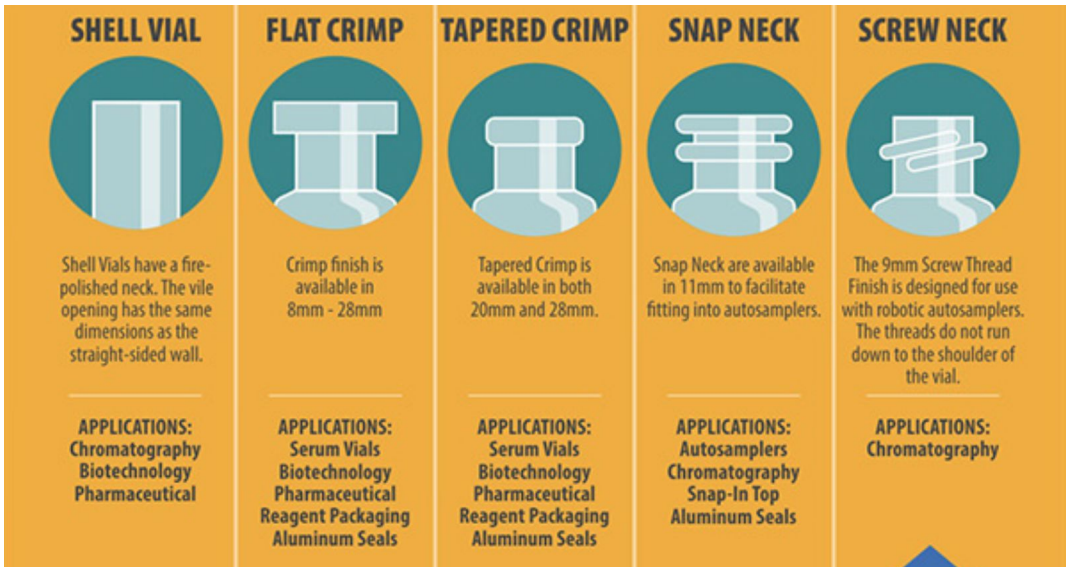


Figure 4: different types of neck finish styles, with their applications and specifications. Source: O.Berk[99]

[98] "PP-PET-Solid-Liquid.Pdf," accessed June 12, 2020,

[99] "How Do You Spec a Glass Vial? Infographic Step-by-Step by O.Berk," accessed June 12, 2020, https://www.oberk.com/packaging-crash-course/infographic-how-to-spec-a-vial.

What does the manufacturing process look like?

Vial forming from glass tubes is a manufacturing process laden with numerous challenges, due to the stringent needs of the pharmaceutical packaging industry. Manufacturing vials entails several steps: glass tube feeding, the glass forming process (heating, neck and shoulder forming, cutting, bottom forming), annealing (heat treatment to remove internal stresses and toughen vial), cosmetic inspection, packaging, and transport. Here is an example video of a set of state-of-the-art vials forming machines.[100]

Companies that dominate vial production include Schott, Nippon Electric Glass, Nipro and Corning Inc. (these companies specialize in borosilicate glass, favored by the pharma industry because it does not react with contents), as well as West, SGD Pharma, Gerresheimer, and Stevanato Group. Currently, drugmakers buy vials for less than 11.26 cents apiece. Using the Stevanato Group website, it is possible to get a quotation for the cost of manufacturing vials. Cost is not the only issue — leaders in the industry worry about vial shortages. Currently, the industry supplies about 50 billion medical borosilicate glass containers per year, of which 15-20 billion are medical vials, even without a pandemic. Schott Chief Executive Frank Heinricht speculates Schott, and its peers will manage to add about 1 billion vials likely needed for a global immunization effort. That would require a vial to be used for multiple injections.[101] Beyond cost and quantity, an additional relevant consideration is manufacturing speed.

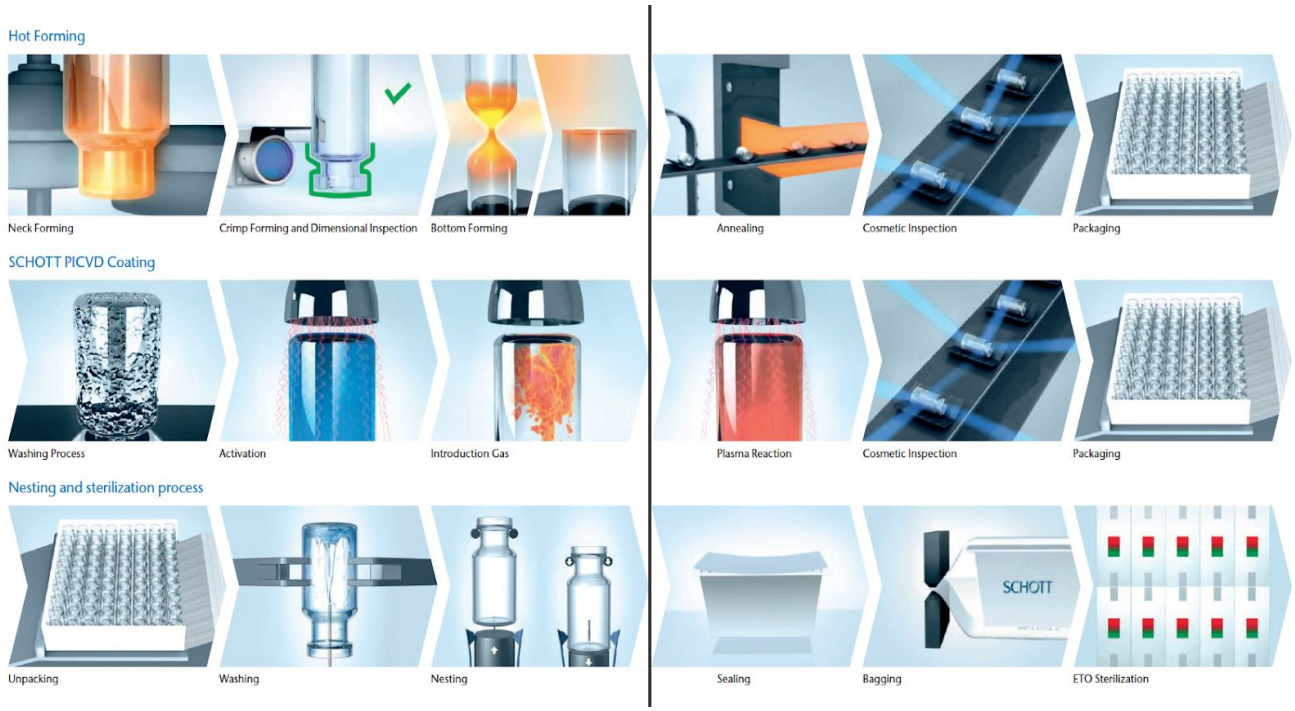


Figure 6: flow chart of the manufacturing process for glass vials. Source: SCHOTT Pharmaceutical Packaging[102]

[100] "Vials Forming Lines - Stevanato Group," accessed June 12, 2020, https://engineering.stevanatogroup.com/products/glass-processing/vials-forming-lines/.
[101] "Exclusive: Bottlenecks? Glass Vial Makers Prepare for COVID-19 Vaccine," *Reuters*, June 12, 2020, https://uk.reuters.com/article/uk-health-coronavirus-schott-exclusive-idUKKBN23J0TP.
[102] "Glass Vials | SCHOTT Pharmaceutical Packaging | SCHOTT North America," accessed June 4, 2020, https://www.us.schott.com/pharmaceutical_packaging/english/products/vials.html.

Packaging

There are a number of packaging options, including shrink wrap modules, tray pack, carton, palletized, and cell pack as seen in the image below.

Figure 5: different ways of packaging vials for shipping. Source: O.Berk[103]

Government Regulations & Quality Control

The main regulatory body for pharmaceutical packaging in the US, including vials, is the Food and Drug Administration. FDA 21 Code of Federal Regulations (CFR) part 211 covers the Current Good Manufacturing Practice (CGMP) for pharmaceutical packaging.[104] Subpart E of 21 CFR 211 states that:

- All procedures must be recorded in writing
- Components and closures must be handled in such a way that prevents contamination
- Bagged or boxed components and closures can't be stored on the floor
- Each container or grouping of containers for components or closures must be identified with a distinctive code for each lot in the shipment, and each lot must be identified by its status (ex. Approved, rejected, quarantined).
- Each container or grouping of containers that holds components or closures must be visually examined for labeling and damage. They must also be tested.

The World Health Organization also provides best practices for pharmaceutical packaging and drug containers, including vials, though these are generally non-binding recommendations.[105] National regulatory bodies take precedence over the WHO best practice standards.

---

[103] "How Do You Spec a Glass Vial? Infographic Step-by-Step by O.Berk."
[104] "CFR - Code of Federal Regulations Title 21," accessed June 12, 2020, https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=211&showFR=1&subpartNode=21:4.0.1.1.11.5.
[105] "GuidelinesPackagingPharmaceuticalProductsTRS902Annex9.Pdf," accessed June 12, 2020, https://www.who.int/medicines/areas/quality_safety/quality_assurance/GuidelinesPackagingPharmaceuticalProductsTRS902Annex9.pdf?ua=1.

Further Research

This memo provides a basic overview of vials. In order to complete the vial production process, however, there are a number of other important questions to answer. How does the vial compare to alternatives, such as pre-filled syringes, ampoules, and cartridges? Where are the component materials of a vial sourced from? Where can the vial be produced, and what does the supply chain look like? What kinds of professional expertise are needed? What requirements do the vials need to satisfy (i.e., FDA, customs restrictions)? How should the vial be priced? The answers to many of these questions will be uncertain until the nature of the API is determined. However, these questions are worth considering early in order to avoid potential gaps in the eventual manufacturing of vials.

2. What does the vial manufacturing process look like?

The primary goal of this memo is to understand what the vial manufacturing process looks like in aims of nearing our research goals, which are 1) to create a comprehensive overview of the vial manufacturing process, 2) to identify potential bottlenecks in the manufacturing process, and 3) to lay out what a manufacturing facility (in Chile) might look like.

Manufacturing Process

Glass Vials

The purpose of this memo is to elaborate on the manufacturing process for vial components. We will assume the vial is made of Type I borosilicate glass, since this is the industry standard. Below are two flowcharts of the glass vial production line:

Figure 1: micro flow chart of the manufacturing process for glass vials. Source: SCHOTT Pharmaceutical Packaging[106]

[106] "Glass Vials | SCHOTT Pharmaceutical Packaging | SCHOTT North America," accessed June 4, 2020, https://www.us.schott.com/pharmaceutical_packaging/english/products/vials.html.

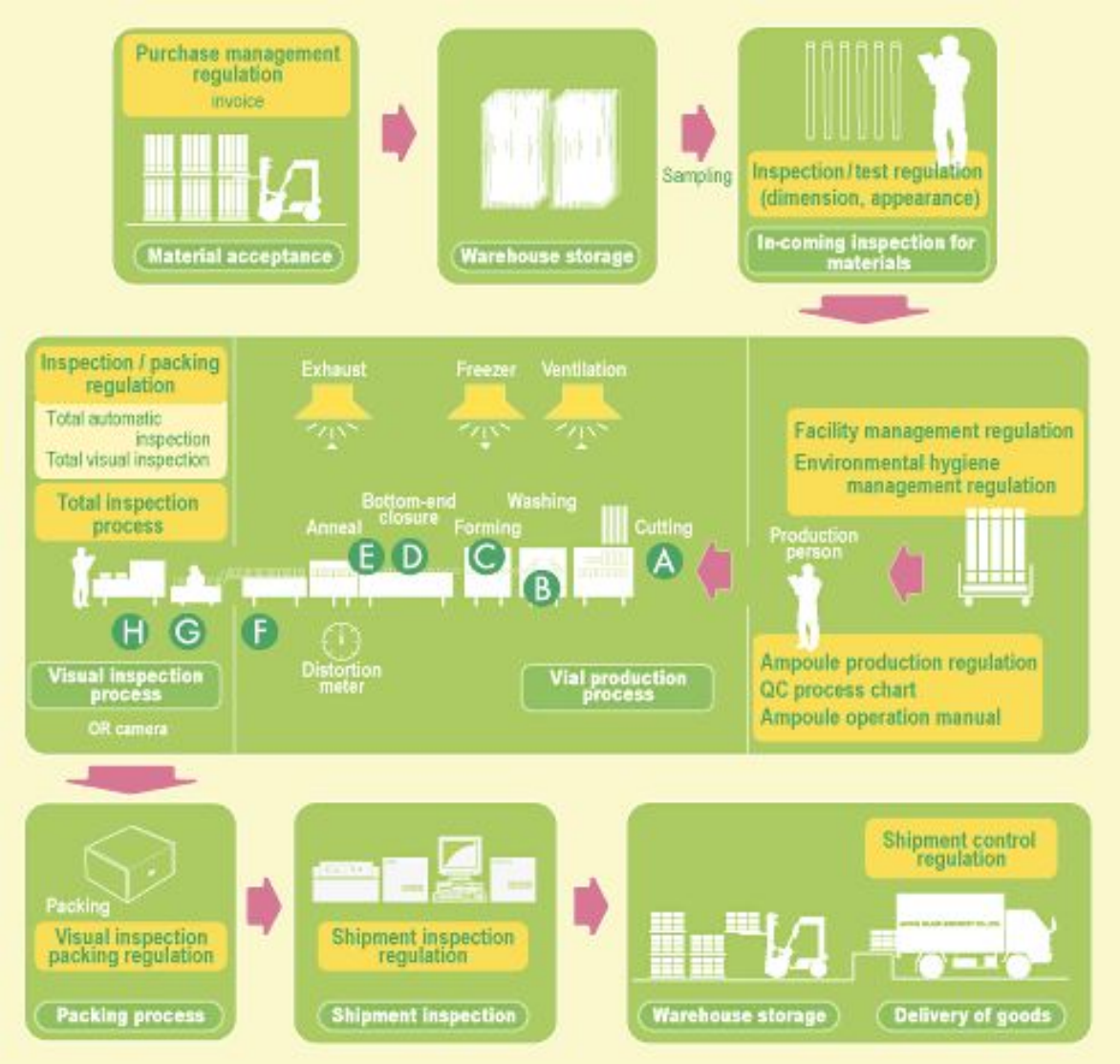


Figure 2: macro flow chart of the manufacturing process for glass vials. Source: Japan Glass Industry.[107]

Although the manufacturing process varies by company, common procedures include:[108]

- **Purchase management regulation**
    - Accept vial component materials, including glass and manufacturing equipment
    - Receive and pay invoice
    - Inspect material quality
    - Store in warehouse until ready for manufacturing
- **Inspection test regulation**
    - Sample materials to inspect for proper dimensions and appearance

[107] "Japan Glass Industry Co., Ltd.: Vial Manufacturing Process," accessed June 25, 2020, http://www.jgi-jp.com/english/frameset/fset03.htm.
[108] *Pacific Vial Manufacturing - Factory Made*, accessed June 25, 2020, https://www.youtube.com/watch?v=m7Sfxhrq-9o.

- **Facility management / Environmental hygiene management regulation**
    - Ensure facilities are well-equipped to produce vials. This may include inclusion and inspection of an automatic water demineralizer, which always supplies constant pure water, and an air-conditioning system, fully equipped with ventilation and exhaust apparatus in order to keep the inside of the factory clean.

Figure 3: Automatic water demineralizer.
Source: Japan Glass Industry.[109]

Figure 4: Air-conditioning system.

- **Vial production process**
    - **Glass tube feeding and cutting**
        - Decide whether glass tube feeding process will be vertical or horizontal
        - Assemble tall glass tubes around four feet in length
        - Drop glass tubes into pre-heater (~1500 degrees F) so they can be heated and cut from the bottom-up into smaller pieces to make vials
        - Rotate tubes past a natural gas burner (~2300 degrees F)
        - Since the natural gas burner closes up the mouth of the tube, use third burner that shoots up a flame to re-open the mouth

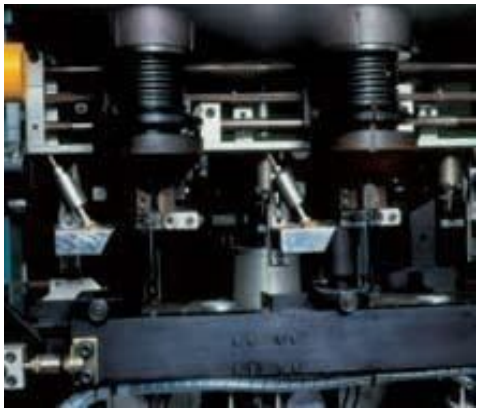


Figure 5: chill cutting of glass tubes.

    - **Washing:** Some companies choose to wash and dry the cut tubes before the glass forming process.

[109] "Japan Glass Industry Co., Ltd.: Vial Manufacturing Process." (All subsequent images in this section are sourced from the Japan Glass Industry)

Figure 6: Ultrasonic washing and drying equipment.

- **Neck and shoulder forming**
  - Preheat top of vial to ~1500 degrees F until the vial is soft enough to start collapsing into a neck on its own
  - Move vial out of flame and in between two heat resistant steel rollers that shape the soft glass, almost like clay on a potter's wheel
  - Use a second set of rollers to add the threads to the neck
  - Transport vials to camera station for inspection, ensuring neck and cap will match

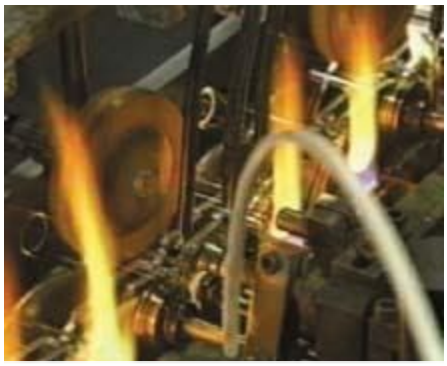


Figure 7: neck and shoulder forming

- **Bottom forming**
  - Use flame to cut off bottom of vial from rest of the long glass tube
    - Note: just like the mouth, the liquid glass from the cut seals off the opening
  - To flatten out the bottom, shape the vial the opposite direction
  - Shoot a strong shot of air into the vial to force the soft bottom to bubble up into a dome. This way, gravity can pull the glass back down, letting the glass come together in a stronger pattern than if the glass were forced to settle down
  - Before the dome sets, heat the class again to allow the dome to collapse down into a flat bottom.
  - Pass the vial through a metal arm for inspection. If the vial is apple to pass by

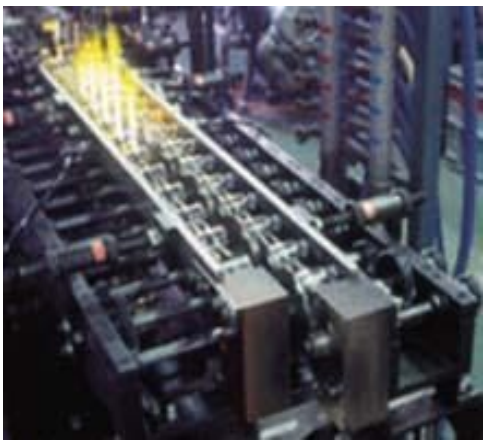


Figure 8: Bottom-end closure.

without touching the arm, then the bottom is flat, and the vial won't tip over.

- **Annealing**: Use a heat treatment to remove internal stresses and toughen vial

Figure 9: Annealing.

- **Cosmetic inspection**

Figure 10: From annealing to inspection.

Figure 11: Automatic dimension and appearance inspection equipment.

- **Packaging**
  - When the glass cools, pluck the finished vial off the line using a robotic arm
  - Carry the vials via conveyor belt into a silk screen machine that prints the logo on the vial
- **Visual inspection packing regulation**
  - Once the tubes are completed, undergo multiple tests and inspections to ensure that they comply with quality standards. A visual inspection is conducted by an advanced, high-resolution camera system for defect removal. Once formed and cut to the correct shape, the dimensions are validated.[110]
- **Shipment inspection regulation**
- **Shipment and Transport**

[110] "The Glass Bottle Manufacturing Process," accessed June 25, 2020, http://www.qorpak.com/pages/glassbottlemanufacturingprocess.

Rubber Stopper

The following graphic shows the manufacturing process of butyl rubber stoppers.[111]

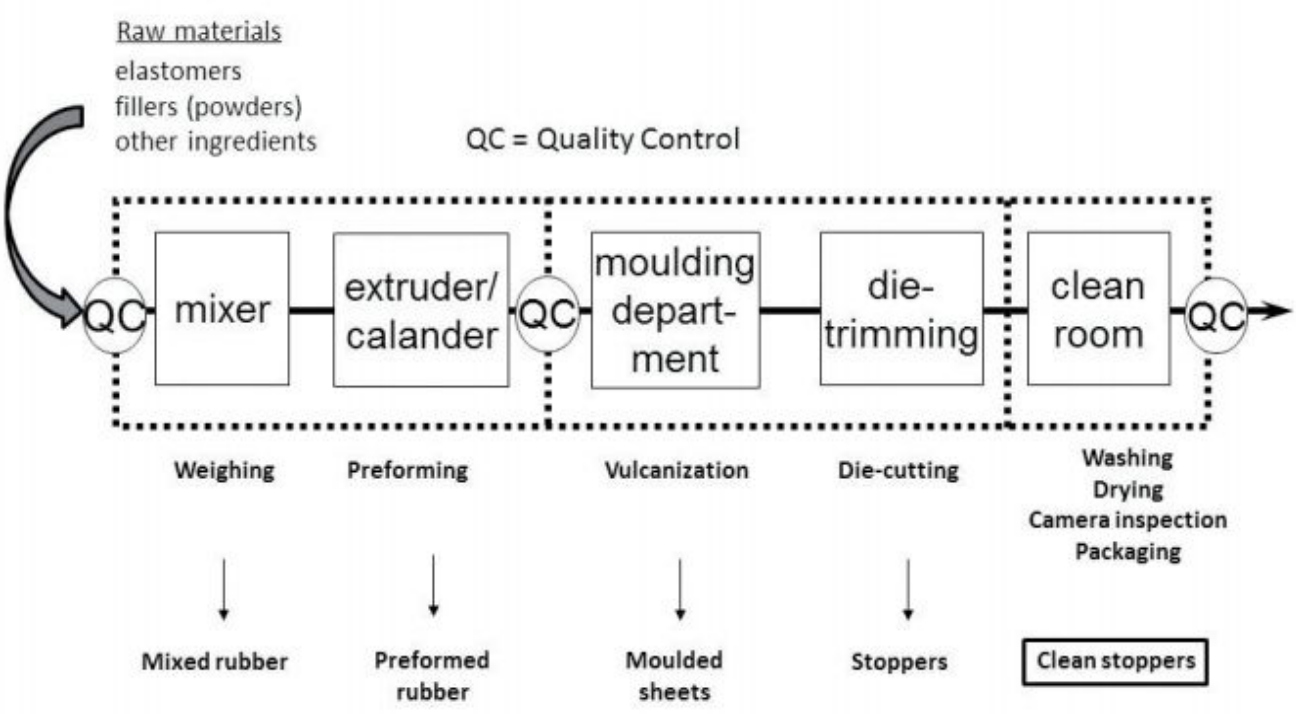


Figure 12: The graphic shows the manufacturing process of rubber stoppers. The physical location and machinery used are inside the dotted lines, the steps of the process are listed below, and below the arrows are the outputs of each step.

The steps of the manufacturing process are

- Weighing: raw materials like the elastomer, filler powder, and other ingredients are combined using a mixer, and then weighed
- Pre-forming: mixed rubber is put into an extruder or calendar, and preformed
- Vulcanization: preformed rubber is vulcanized and transformed into molded sheets
- Die-cutting: the molded sheets of rubber are cut into individual stoppers
- Final steps: the finished stoppers are transported to a clean room, where they are washed, dried, inspected, and packaged for transportation

Aluminum Cap

The most popular aluminum cap design, and the most pertinent to our needs, is the aluminum cap with a flip off or tear off center tabs/button. Aluminum caps are manufactured from flat rolled aluminum, through the process shown below:

[111] Renaud Janssen, "Elastomere Teile Für Parenteralia," 2013, 7.

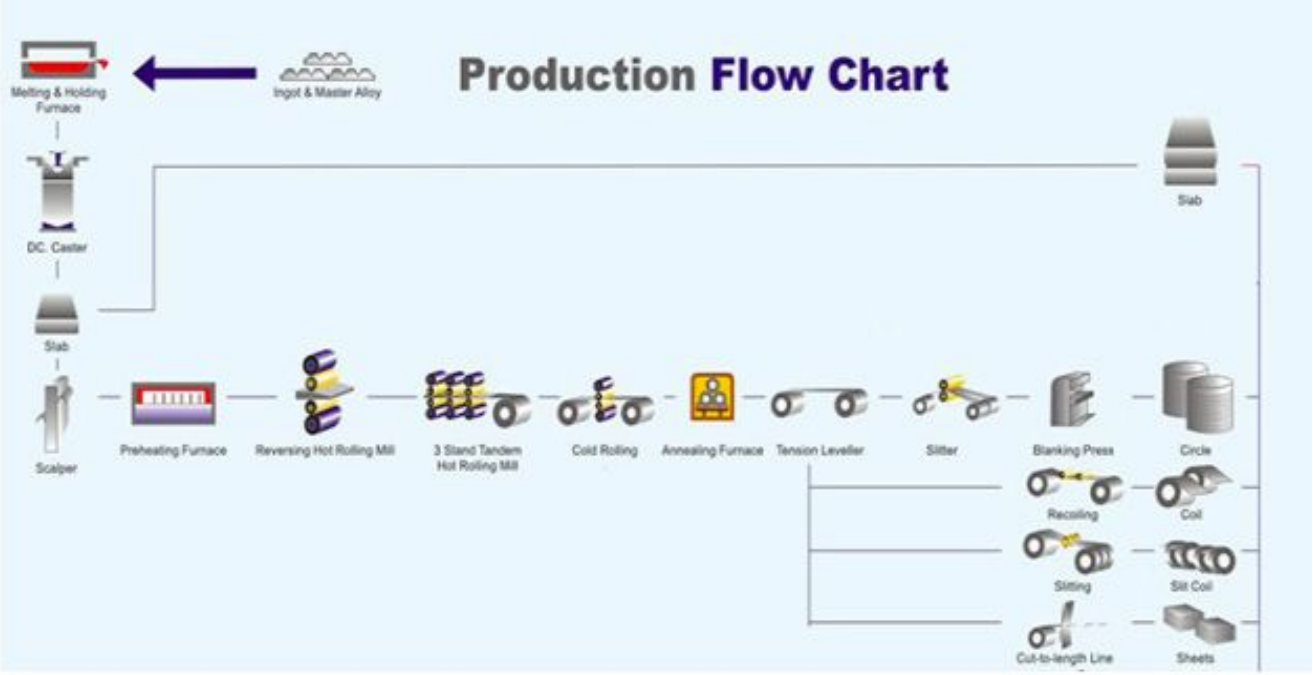


Figure 13: Diagram from Signi Aluminum.[112]

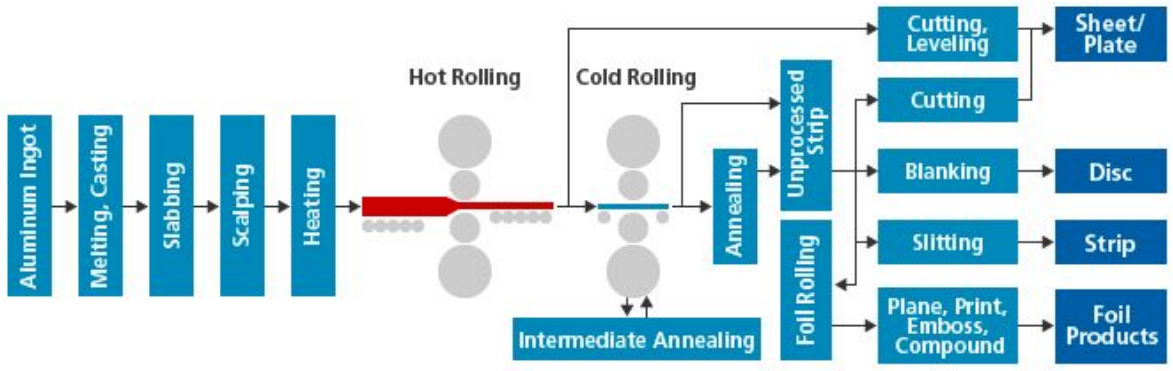


Figure 14: Diagram from UACJ.[113]

The above diagrams show the following steps in the manufacturing process:

- Melting: Aluminum ingot (pure aluminum) is melted down, treated, and cast into aluminum slabs
- Scalping: Aluminum slab is shaved down in a scalping machine, and then pre-heated
- Hot Rolling: The aluminum is rolled down in a mill to a specific thickness, producing hot rolled coils

[112] "Production Process," accessed June 25, 2020, http://www.aluminum-cap-closure-sheet.com/Production_Process/.
[113] "Flat Rolling : UACJ Corporation," UACJ Corporation, A major Global Aluminum Group, accessed June 27, 2020, https://www.uacj.co.jp/english/techno/production/roll.htm.

- Cold rolling: Hot coils are then rolled to the desired thickness, and treated in an annealing furnace to achieve desired strength
- Levelling: A tension leveller is used to uncoil cold aluminum
- Coating: Aluminum can be coated in color, if applicable (see figure 13)
- Printing line: Coated aluminum is punched into desired shape and size using a blanking machine, to make a cap

Major Takeaways

- The glass vial manufacturing process entails a series of precise heating mechanisms. While glass is the only primary material being manipulated, the machinery used to heat the glass is more involved.
- Inspection occurs systematically after each major step in the manufacturing process. For example, in the glass vial production process, inspection occurs when accepting the purchase of materials, checking the facility management and environmental hygiene before vial production, after the neck and bottom forming processes, after annealing, and after packaging.
- Generally, the most common construction of vial parts is: Type I borosilicate glass vials, halobutyl rubber serum or lyophilized drug stoppers, and aluminum flip-off crimp caps with plastic flip-off buttons.
- The manufacturing process for glass vials does not seem highly specialized. Many companies that produce glass, rubber, and aluminum products generally use similar processes.

Further questions

Our further questions include: where can we find more specialized information on vial cap manufacturing processes and vial production machinery? What do the details of internal quality inspection look like? Do specific aluminum cap styles work better with serum or lyo-specific stoppers? With this new knowledge of the glass vial manufacturing process, our next memo will ask: "What does the vial supply chain look like?" and will serve as a natural continuation of this report. Stay tuned.

3. What does the vial supply chain look like?

Continuing off of the second memo investigating the vial manufacturing process, the primary goal of this memo is to understand what the vial supply chain looks like in aims of nearing our research goals, which are 1) to create a comprehensive overview of the vial manufacturing process, 2) to identify potential bottlenecks in the manufacturing process, and 3) to lay out what a manufacturing facility (in Chile) might look like.

Introduction

The purpose of this memo is to elaborate on the supply chain for vial components. We will assume the vial is made of Type I borosilicate glass and the stopper is made of bromobutyl rubber with an aluminum cap, since this is the industry norm. Below is an overview of the vaccine manufacturing process.

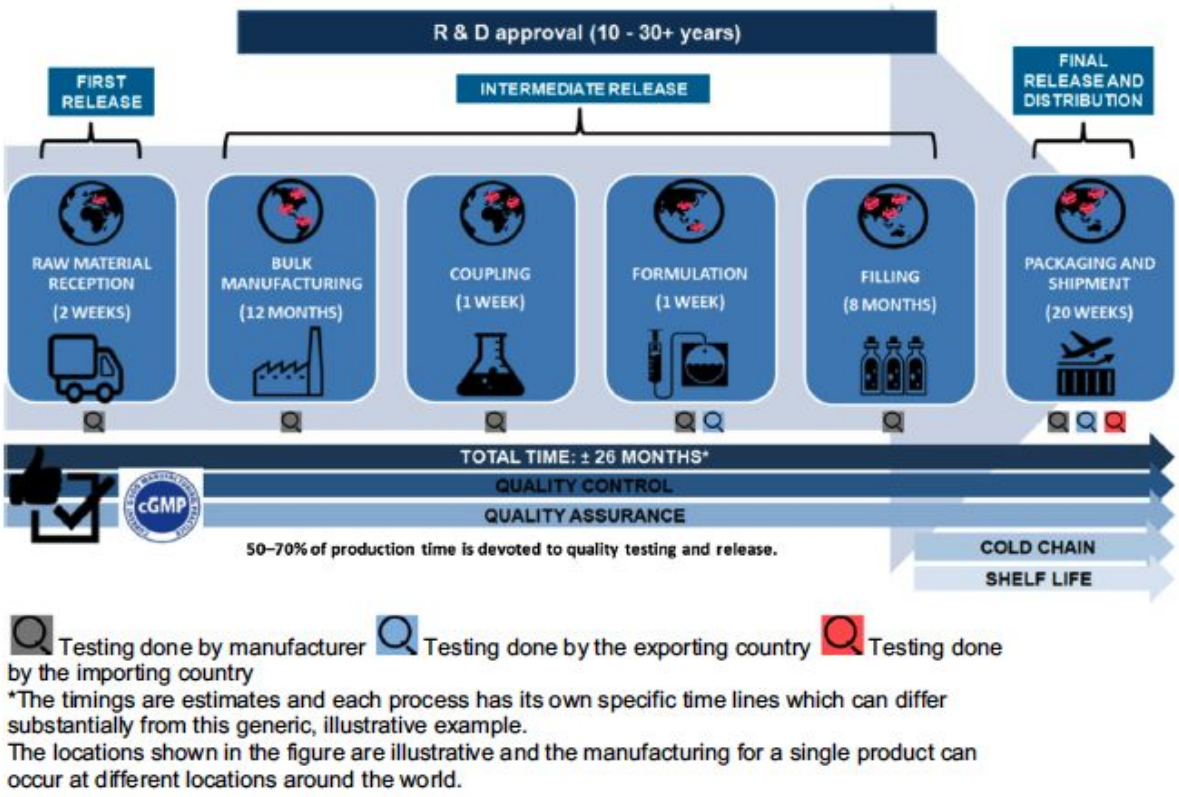


Figure 1: Steps in vaccine manufacturing and parallel testing of quality at all stages. Source: Preiss et al.[114]

Supply chain

Vial supply chain

Material	Source	Current Events
Borosilicate glass tubes are hollow pieces made of borosilicate glass. Borosilicate glass is a heat and shatter resistant material that is composed of silica sand and at least 5% boric oxide. Borosilicate glass is created by	Key Manufacturers[116] Corning Incorporated (US) Nipro Corporation (Japan) SGD S.A (France) Stölzle-Oberglas GmbH (Austria)	Corning, the U.S. glassmaker based in New York, is tapping a $204 million government contract to help accelerate construction of a 2,000-degree furnace in New Jersey that will exude molten glass into lengths of medical-grade tubing

[114] Scott Preiss et al., "Vaccine Provision: Delivering Sustained & Widespread Use," *Vaccine* 34, no. 52 (2016): 6665–6671, https://doi.org/10.1016/j.vaccine.2016.10.079.
[116] "Pharmaceutical Glass Packaging Market | Industry Report, 2019-2025," accessed July 24, 2020, https://www.grandviewresearch.com/industry-analysis/pharmaceutical-glass-packaging-market.

combining and melting boric acid, silica sand, soda ash, and alumina. Also, borosilicate glass is commonly referred to as Pyrex, this type of glass is used for the manufacturing of products that handle strong acids and alkalis because of its resistance to breakage and its high chemical resistance.[115]	Bormioli Pharma S.r.l (Italy) West Pharmaceutical Services, Inc. (US) Schott AG (Germany) Gerresheimer AG (Germany) Shandong Medicinal Glass Co., Ltd. (China) Beatson Clark (England) Ardagh Group S.A (Ireland) Arab Pharmaceutical Glass Co. (Egypt) Piramal Enterprises Ltd. (India) Şişecam Group (Turkey) <u>Geographical Location</u> The top boric acid exporting countries include the United States, Turkey, Russia, Chile, and Peru.[117] The top silica sand exporting countries include the United States, Australia, Belgium-Luxembourg, Germany, and Saudi Arabia.[118]	hundreds of feet long.[119] Stevanato has received an order from the global nonprofit Coalition for Epidemic Preparedness Innovations (CEPI) for 100 million vials that can contain enough vaccine for 20 doses each, enough for 2 billion shots.[120] The U.S. government has signed contracts of $204 million with Corning and $143 million with an Alabama company, SiO2, which makes specialized plastic pharmaceutical vials that the company says withstand breakage and do not require manufacturing by using the extreme heat of a glass furnace. SiO2 will provide 120 million vials for U.S. domestic priorities by the end of 2020 and as many as 1 billion by April 2021 — which could satisfy a very large portion of the surge in global demand. The company recently announced a $163 million expansion of its manufacturing plant in Auburn, Ala. In March, SiO2 was running at a pace of 14 million vials per year. It expects to hit a pace of 120 million a year by December.[121]

[115] *Borosilicate Glass Manufacturers, Suppliers, and Industry Information*, 2019, https://www.youtube.com/watch?time_continue=2&v=zz5pCXTDZx0&feature=emb_logo.
[117] "Oxides of Boron, Boric Acids (HS: 281000) Product Trade, Exporters and Importers," accessed July 1, 2020, https://oec.world/en/profile/hs92/oxides-of-boron-boric-acids.
[118] "Silica Sands and Quartz Sands (HS: 250510) Product Trade, Exporters and Importers," accessed July 1, 2020, https://oec.world/en/profile/hs92/silica-sands-and-quartz-sands.
[119] Christopher Rowland, "A Race Is on to Make Enough Small Glass Vials to Deliver Coronavirus Vaccine around the World," *Washington Post*, accessed July 17, 2020, https://www.washingtonpost.com/business/2020/07/13/coronavirus-vaccine-corning-glass/.
[120] Rowland.
[121] Rowland.

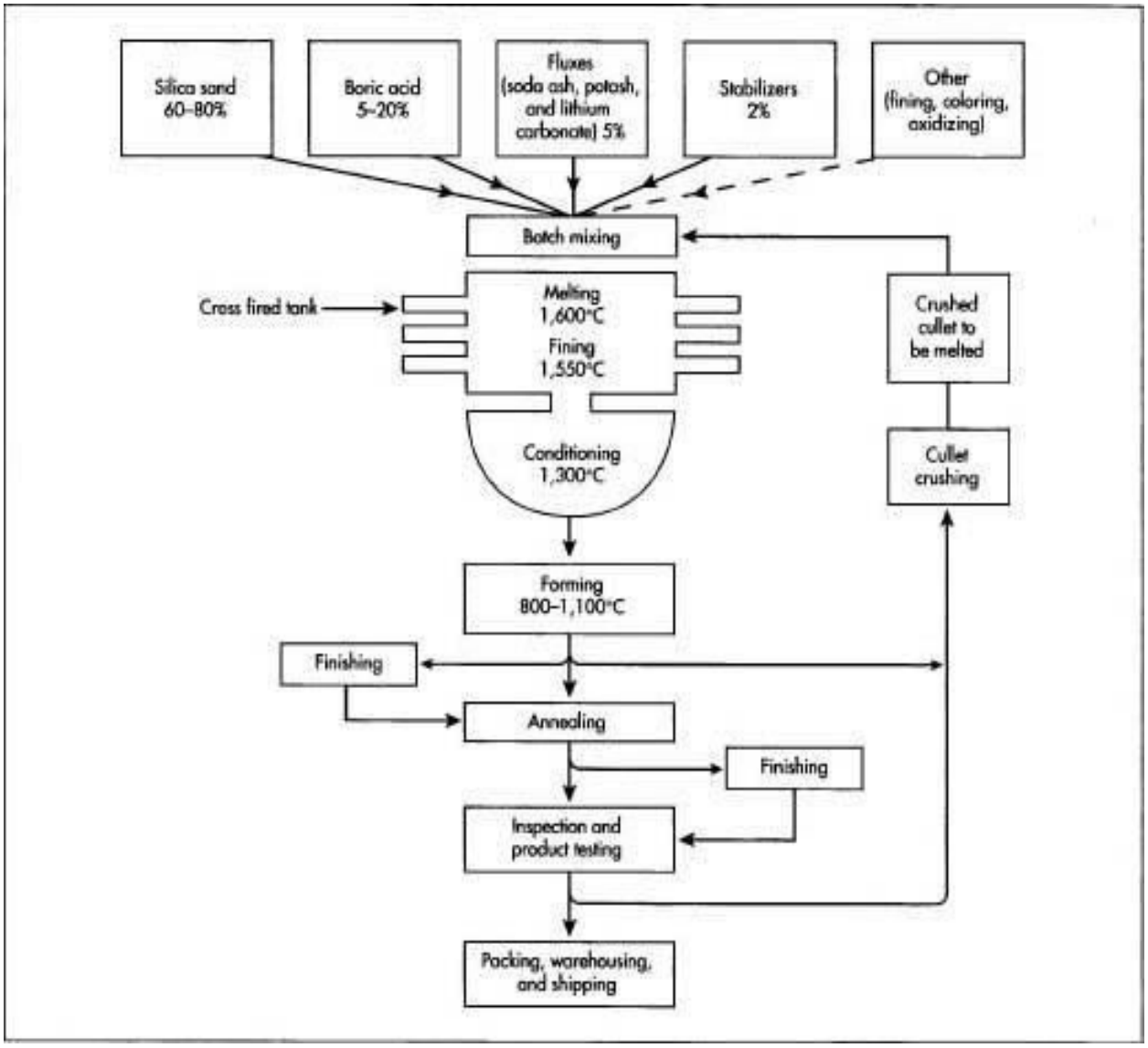


Figure 2: diagram of the production of borosilicate glass, or Pyrex.
Source: How Products Are Made.[122]

[122] "How Pyrex Is Made - Material, Production Process, Manufacture, Making, History, Used, Processing, Components," accessed July 1, 2020, http://www.madehow.com/Volume-7/Pyrex.html.

Stopper supply chain

Material	Source	Current Events
Bromobutyl rubber - Bromobutyl rubber is a type of elastomer (synthetic rubber) that is made by combining bromine with butyl rubber. **Butyl rubber** is made by combining isoprene with isobutylene, both of which are obtained through thermal cracking of natural gas, or lighter fractions of petroleum.[123] **Bromine** is a halogen naturally found in salt deposits and brines. Ocean water is the biggest commercial source of bromine.[124]	<u>Companies</u> Some of the top manufacturers of butyl rubber are Exxon Mobil, Lanxess, Royal, and Reliance Sibur.[125] **Exxon Mobil** is an American company with manufacturing locations in Australia, China, India, Japan, Singapore, Thailand, Belgium, France, Germany, Italy, the Netherlands, the United Kingdom, Saudi Arabia, Canada, Mexico, the United States, and Brazil.[126] **Lanxess** is a German company that has manufacturing facilities in the United States, Belgium, South Africa, India, and Germany.[127] **Royal Rubber** is an American company with a manufacturing facility in the United States.[128] **Reliance Sibur** is a partnership between the Indian corporation Reliance, and the Russion petrochemical company Sibur. They have a manufacturing facility in India.[129] Companies that specifically make pharmaceutical rubber stoppers include West, Aptar Pharma, and others. These companies often offer complete vial packages, which include the vial, cap and stopper.[130] **West** produces rubber stoppers from their facilities in the U.S., Denmark, England, France, Germany, Ireland, Israel, Italy, Serbia, Spain, Australia, China, India, Korea, Singapore, Puerto Rico, Brazil, Argentina, and Colombia.[131] The leading companies in bromine extraction and production are Israel Chemicals Ltd., Albemarle,	

[123] "Butyl Rubber | Chemical Compound," Encyclopedia Britannica, accessed June 12, 2020, https://www.britannica.com/science/butyl-rubber.
[124] "Bromine | Properties, Uses, & Facts," Encyclopedia Britannica, accessed July 1, 2020, https://www.britannica.com/science/bromine.
[125] "Butyl Suppliers," accessed July 1, 2020, http://polymerdatabase.com/Polymer%20Brands/Butyl.html.
[126] "Where We Operate | ExxonMobil Chemical," accessed July 25, 2020, https://www.exxonmobilchemical.com/en/exxonmobil-chemical/about-us/where-we-operate.
[127] "LANXESS - Technical Centers - Production Facilities," accessed July 25, 2020, https://techcenter.lanxess.com/ruc/americas/en/service/12599/uniarticle.jsp?docId=12599.
[128] "Royal Rubber - Rubber Supplier," accessed July 25, 2020, https://www.royalrubber.com/location.cfm.
[129] "Reliance Sibur," accessed July 25, 2020, http://www.reliancesibur.com/butyl-rubber.html.
[130] "Butyl Suppliers."
[131] "Locations - West Pharma," accessed July 20, 2020, https://www.westpharma.com/global-locations.

	Jordan Bromine Company, and Lanxess.[132] Geographical Location Bromine is found primarily in Jordan, Israel and the United States. Bromine can also be derived from a rare insoluble mineral called bromyrite, which can be found in Chile.[133]	

Cap supply chain

Material	Source	Current Events

[132] Reportlinker, "Global Bromine Industry," accessed July 1, 2020, https://www.prnewswire.com/news-releases/global-bromine-industry-300978932.html.
[133] "Bromine | Properties, Uses, & Facts."

Aluminum - in order to get aluminum ingot, aluminum must first be produced from bauxite, a mineral obtained through strip mining. Bauxite is combined with sodium hydroxide, undergoes the Bayer process, and melted down to produce alumina, which is combined and processed with cryolite and oxygen through the Hall-Heroult process to produce pure aluminum.[134] 4 lbs. bauxite produces 1 lb. of aluminum.[135] Molten aluminum is then poured into a mold to be cast into ingots.	<u>Companies</u> Bauxite--the three leading producers of bauxite are Australia, China, and Guinea. The top 5 bauxite mining companies are Alcoa, Rio Tinto, Hydro, The Aluminum Corporation of China, and Compagnie des Bauxites de Guinea (CBG).[136] One of the major companies that makes aluminum caps is EMA Pharmaceuticals, a French company with one production facility in France.[137] <u>Geographical Location</u> Bauxite is a relatively common and abundant resource. The top aluminum exporting countries include Canada, United Arab Emirates, Russia, India, and Norway.[138]	EMA has made a deal with GSK to provide aluminum caps for future vaccines. It already manufactures 1 billion caps per year and is planning on increasing its output by 10-20% to meet demand.[139] Bauxite mining has been causing air pollution and public health issues in Guinea, according to a study conducted by the Lamont-Doherty Earth Observatory.

Bottlenecks

Transport

One of the first challenges in the manufacturing process is long lead times on production. From the time raw materials are received, vaccines can take from 10 to 26 months before they are ready for shipping. A significant amount of this time (up to 70%) is dedicated to the completion and analysis of quality control testing.[140]

Many steps in the supply chain involve transport of delicate materials. Some examples of transport include shipment of raw materials, glass tubes, and finished vials. As noted in the first memo, there are a

[134] "Primary Production | The Aluminum Association," accessed June 30, 2020, https://www.aluminum.org/industries/production/primary-production.
[135] "Primary Production | The Aluminum Association."
[136] "Top Five Bauxite Mining Companies in the World," alcircle, accessed June 30, 2020, https://www.alcircle.com//news/top-five-bauxite-mining-companies-in-the-world-26315.
[137] "Location | Ema Pharmaceuticals, Aluminum Crimp Caps for Pharmaceutical Containers," accessed July 25, 2020, http://emapharma.com/en/location.
[138] "Raw Aluminium (HS: 7601) Product Trade, Exporters and Importers | OEC - The Observatory of Economic Complexity," accessed June 30, 2020, https://oec.world/en/profile/hs92/157601/.
[139] Centre France, "Industrie Pharmaceutique - A Lailly-En-Val, EMA Pharmaceuticals Travaille Déjà Pour Le Vaccin Anti-Coronavirus," www.larep.fr, June 27, 2020, https://www.larep.fr/lailly-en-val-45740/actualites/a-lailly-en-val-ema-pharmaceuticals-travaille-deja-pour-le-vaccin-anti-coronavirus_13804870/.
[140] Preiss et al., "Vaccine Provision."

number of packaging options to aid safe transportation, including shrink wrap modules, tray pack, carton, palletized, and cell pack.

Distribution of a vaccine can be classified into three main components: primary distribution by the manufacturer of the country, secondary distribution by government agencies or local distributors, and finally the storage and use of the vaccine at a clinic or pharmacy.[141]

Standardization of glass tube, stopper, cap specifications

In the case that different companies are responsible for producing the vials, stoppers, and caps, there must be clear and timely communication to standardize the specifications and design of the component parts. The specifications as determined by pharma analytical tests, along with lot samples, are provided to authorities to independently verify before approving the distribution of vaccine. The national authority where the vaccine is produced confirms that the lot meets specifications and may undertake further independent tests. The country authority which will receive the lot also confirms the specifications and may undertake independent tests on the lot awaiting release. The industry seems to be settling on 10-milliliter vials, capable of holding eight to 15 doses (in order to conserve glass supply), as the most common standard.[142]

In addition, though it seems that many companies are able to produce rubber stoppers and aluminum caps, some of the largest pharmaceutical packaging companies (such as West) make their own and have patents, and thus might be unwilling to work with their competition. So far in our research, we have been unable to find relative production quantities.

Lack of public information about stopper manufacturing

There seems to be a lack of non-highly technical information about the stopper supply chain. Two remaining questions include the role of petroleum in the production of stoppers, and the relationship between the petroleum and pharma industries.

Limited quantity of raw materials

Given the unprecedented quantity of vials anticipated for a COVID-19 vaccine, there may be a shortage of raw materials and a potential need to redistribute materials from other products and industries. The following graphic shows the pre-COVID-19 projected increase in demand for various raw materials since 2017.[143]

[141] Preiss et al.
[142] Rowland, "A Race Is on to Make Enough Small Glass Vials to Deliver Coronavirus Vaccine around the World."
[143] "Pharmaceutical Packaging Market," accessed July 20, 2020, https://secure.livechatinc.com/.
Professional expertise https://www.zippia.com/level-vial-inspector-jobs/

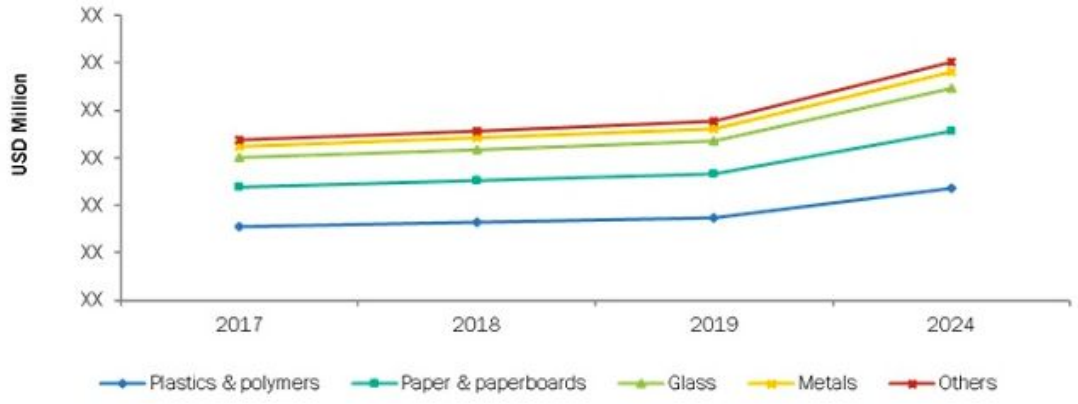


Figure 3: This graph depicts the increase in demand for pharmaceutical packaging raw materials, projected out to 2024. It was created prior to the spread of COVID-19.

Trade restrictions
Countries with specialized areas in the supply chain might be reluctant to contribute materials and expertise to the supply chain if not promised benefits in return. In addition, there may be customs restrictions preventing the flow of goods from one country to another within the supply chain.

Professional expertise
Much of the manufacturing know-how exists in private commercial entities. For example, a production worker in a vial manufacturing facility may need to be trained to conduct the following tasks: preparing machines for use by choosing appropriate attachments and controls, working towards achieving set goals and KPIs, recording production data as required, examining final products for imperfections, and ensuring the work environment is clean and safe by complying with OH&S requirements. Additional roles may include pickers and packers and the assembly line, process workers in particular production processes, forklift drivers, and machine operators and inspectors.[144] It may be necessary to consult these corporations to secure more expertise about the vial manufacturing process.

Machinery parts and equipment
Although the manufacturing processes for the vial, stopper, and cap seem relatively standardized, more research is necessary in order to determine the best practices for building and operating machinery to produce vials at scale. Many details must be considered — for example, inspection check points, regular cleaning and cooling of machinery, and temperature control of facilities.

Moreover, many vaccines require unique processes and techniques. For example, equipment and processes required to produce bacterial or viral vaccines are often incompatible with each other; one relies on bacterial fermentation bioreactors and the other on large scale eukaryotic cell culture or chicken embryonic fibroblasts. Therefore, it is rarely possible to share a bulk facility across many products; each

[144] "Here's How To Become A Level Vial Inspector In 2020," May 18, 2020, https://www.zippia.com/level-vial-inspector-jobs/.

facility is usually custom built for the product. This makes long term forecasting of a vaccine's worldwide demand a critical factor in delivering a sustainable and sufficient supply of vaccine for a global need. It is also why long-term contracts are a preferred way to reduce supply risk on a country-by-country basis.[145]

Production capacity

Leaders in the industry worry about vial shortages. Currently, the industry supplies about 50 billion medical borosilicate glass containers per year, of which 15-20 billion are medical vials, even without a pandemic. More search needs to be done to determine whether there can be substitutions between industries. The job of delivering vaccines to a majority of humans is so vast that global production of pharmaceutical vials needs to be ramped up by 5 to 10 percent within two years, a job the industry says requires immediate preparation and increases in production but is not an insurmountable challenge.[146] Schott Chief Executive Frank Heinricht speculates Schott, and its peers will manage to add about 1 billion vials likely needed for a global immunization effort. However, that would require a vial to be used for multiple injections.[147] This suggests that in order to make single-dose vials, many more vials will need to be produced.

Vial presentation

Single-dose vs multi-dose vs pre-filled syringe. Single-dose vials may be preservative-free and can prevent clinic-level vaccine wastage. However, single-dose vials reduce the capacity for production and increase costs. A facility with the capacity to fill, inspect, and package 1 million units will see a loss of doses if it packages single-dose vials rather than 10-dose vials, because the bottle-neck is on the number of physical units, not the volume of the units.

It is also important that the recipient gets the correct dose of vaccine and both multi-dose and pre-filled syringes are overfilled to ensure practitioners deliver the intended dose. The overfill provided for 10-dose vials is about 16-24% of the total volume, compared to 28-44% for prefilled syringes. Estimates of filling capacity loss as a result of moving from multi-dose to single-dose vials may be as high as a 90% reduction in doses.

Although pre-filled syringes offer a convenient presentation for the practitioner and patients, their use presents challenges to manufacturing and distribution, with both the rate of production, space required to ship, and store and the absolute number of available doses being impacted.[148]

Packaging requirements. Most countries have their own product information and may have requirements around what information is to be displayed on the external packaging, and the total packaging process if often country specific adding to costs. This means that supply disruptions in one country may not instantly be dealt with by moving products from a country with excess supply, as the packaging requirements are likely to be different, and disassembling and repackaging may be required but is not always possible. In addition, the vaccine production process, including identifying suppliers, needs to be approved by local authorities before the

[145] Preiss et al., "Vaccine Provision."
[146] Rowland, "A Race Is on to Make Enough Small Glass Vials to Deliver Coronavirus Vaccine around the World."
[147] "Exclusive: Bottlenecks? Glass Vial Makers Prepare for COVID-19 Vaccine," *Reuters*, June 12, 2020, https://uk.reuters.com/article/uk-health-coronavirus-schott-exclusive-idUKKBN23J0TP.
[148] Preiss et al., "Vaccine Provision."

vaccine is released. It may therefore happen that the available vaccine is not consistent with the current license due to a change in supplier or process improvements that are awaiting approval in a specific country.[149]

Speed

Our record for developing an entirely new vaccine is at least four years— more time than the public or the economy can tolerate social-distancing orders.[150] More research is required to determine the current average speed of vial production, and how much that speed can be ramped up to increase production capacity.

Quality assurance

One major challenge includes ensuring vaccine quality. During the development of a manufacturing process, analytical tools are needed to test the output at multiple stages of production as "release assays." The ultimate goal of analytical testing, related to the quality control of a vaccine's production, is to ensure that the product leaving the factory is equivalent to the product described in the registered label. The specifications as determined by the analytical tests, along with lot samples, are provided to authorities to independently verify before approving the distribution of vaccine. Deviations from the expected specifications often lead to material being rejected, which can impact vaccine supply. Major manufacturers typically run between 100 and 500 different quality control tests to continually assess safety, potency and purity.

Additionally, due to the fact that some companies specialize in certain components while others produce full delivery systems, there is potential for different quality control measures and levels of quality assurance between companies. There are instances where companies have created partnerships so as to maximize their quality assurance. One such example is a partnership between Aptar Pharma, Schott, and Ema. Aptar produces the rubber stoppers, Schott provides the glass vials, and Ema produces the flip cap seal.[151]

Before distribution, quality assurance checks the lot and confirms that all the quality control tests have been completed and that their analysis is accurate and aligned with the process and specifications. The national authority where the vaccine is produced confirms that the lot meets specifications and may undertake further independent tests. The country authority which will receive the lot also confirms the specifications and may undertake independent tests on the lot awaiting release. If all parties have agreed, the lot receives final authorization and is released for distribution.

---

[149] Preiss et al.

[150] Stuart A. Thompson, "Opinion | How Long Will a Vaccine Really Take?," *The New York Times*, April 30, 2020, sec. Opinion, https://www.nytimes.com/interactive/2020/04/30/opinion/coronavirus-covid-vaccine.html.

[151] "Aptar Pharma QuickStart™ Injectables - Nasal Spray Pumps + Other | Pharma," accessed July 25, 2020, https://pharma.aptar.com/en-us/dispensing-solutions/aptar-pharma-quickstarttm-injectables.html.

Test	Objectives	Stage of production process	Typical methods used (non-exhaustive)
Raw materials	• Confirmation of sterility and purity	Before production begins	Chromatography, mass spectrometry, electrophoresis
Vaccine formulation			
Purity	• Identification of impurities	Throughout process	Chromatography, mass spectrometry, electrophoresis
Microbial testing	• Bacteria, such as mycoplasma • Endotoxins • other potential microbial contaminants	Throughout process	Microbiological, Polymerase chain reaction
Identity tests	• Confirmation of molecular structure and size	Bulk	Chromatography, electrophoresis, immunological tests assays such as western blots or immunoelectrophoresis.
Toxicology studies	• Confirmation of inactivation and pyrogenicity	Final product	Animal testing, cell-culture
Physical and chemical properties	• pH • Examination for particulate matter • Quantification of adjuvants	Bulk and final product	Mass spectrometry, electrophoresis, spectroscopy, immunochemistry
Potency	• In vivo or in vitro tests of immunogenicity	Final product	Animal testing, cell-culture, titration assays

Figure 4: Quality control tests applied during the production of vaccines. Source: Preiss et al.[152]

It has been noted that in times of previous public health emergencies, such as the global 2009 H1N1 pandemic, the 2014-15 Ebola outbreaks in West Africa, and the 2014 meningococcal B outbreak on US college campuses, although development timelines were accelerated, rigorous production processes and tests of quality were vitally important due to the reduced about of clinical data, and the vaccines followed stringent regulatory processes designed to ensure safety and effectiveness.[153]

Politics of supply chain

The overwhelming global demand for any successful vaccine is bound to create supply constraints, raising questions about how to allocate doses fairly across the globe. Difficult questions must be addressed regarding how much funding each country provides and how supply would be prioritized. Once vials are filled by manufacturers, a challenge will be distributing volumes of coronavirus vaccine around the country and the world, steering them to viral outbreak hot spots and professions such as health-care workers and emergency responders where they are needed most.[154]

We have already begun to see the emergence of such conflicts. For example, Sanofi, a French pharmaceutical company, came under fire with the French government and public for suggesting that the U.S. had a claim on the first doses of any vaccine given its aid in the vaccine production process. Later, the company assured the French government that any Sanofi vaccine would be distributed in France.[155]

Trade relations also might play a role, as countries and companies export and import raw materials for vial and component production. An example of a possible trade issue occurred earlier this year, as the Trump Administration introduced 10% tariffs on aluminum and aluminum products, which would affect the supply chain of vial closures.[156] In addition, The United States, through the Trump administration's Operation Warp Speed initiative, is locking down supply while prioritizing a boost in domestic

[152] Preiss et al., "Vaccine Provision."
[153] Preiss et al.
[154] Rowland, "A Race Is on to Make Enough Small Glass Vials to Deliver Coronavirus Vaccine around the World."
[155] Noemie Bisserbe, "Sanofi Bows to France's Demand for Coronavirus Vaccine Supplies," *Wall Street Journal*, June 16, 2020, sec. Business, https://www.wsj.com/articles/sanofi-bows-to-frances-demand-for-coronavirus-vaccine-supplies-11592322940.
[156] "Trump's Steel and Aluminum Tariffs Are Cascading out of Control," PIIE, February 4, 2020, https://www.piie.com/blogs/trade-and-investment-policy-watch/trumps-steel-and-aluminum-tariffs-are-cascading-out-control.

manufacturing of medical supplies, many of which are made overseas in Asia (China and India) and Europe.[157]

Regulations

Establishing a new facility can take 5 to 10 years, during which a company must have the facility accredited by various regulatory bodies and demonstrating that the specifications of the product manufactured there meet the label requirements.[158]

There are many regulatory hoops to jump through, including cGMP, corporate, domestic, and international regulations. For example, U.S. and EU packaging regulations state that: "Equipment shall be constructed so that surfaces that contact components, in-process materials, or drug products shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements."[159] In addition to formal regulations, there are informal standards to consider. For example, while the US standard is plastic vials, the European standard is glass.

FDA plays a critical role in protecting the United States from threats such as emerging infectious diseases, including the Coronavirus Disease 2019 (COVID-19) pandemic which has been caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). FDA is committed to providing timely guidance to support response efforts to this pandemic. [160]

CBER is making every effort to review all regulatory submissions (e.g., requests for pre-investigational new drug application (IND) meetings, INDs, and emergency use authorizations (EUAs)) for COVID-19 related treatments as quickly as possible. In order to facilitate this rapid review, please ensure that regulatory submissions contain all of the information necessary to perform a complete review and are submitted in accordance with all regulatory requirements.[161].

The sponsor of a new vaccine product follows a multi-step approval process, which typically includes:

- An Investigational New Drug application
- Pre-licensure vaccine clinical trials
- A Biologics License Application (BLA)
- Inspection of the manufacturing facility

---

[157] David J. Lynch, Jeanne Whalen, and Laurie McGinley, "Trump Takes a First Step toward Returning Medical Supply Chains to the U.S.," *Washington Post*, accessed July 17, 2020, https://www.washingtonpost.com/business/2020/05/19/trump-takes-first-step-toward-returning-medical-supply-chains-us/.

[158] Preiss et al., "Vaccine Provision."

46."Development and Licensure of Vaccines to Prevent COVID-19" https://www.fda.gov/regulatory-information/search-fda-guidance-documents/development-and-licensure-vaccines-prevent-covid-19

47. "Coronavirus (COVID-19) | CBER-Regulated Biologics" https://www.fda.gov/vaccines-blood-biologics/industry-biologics/coronavirus-covid-19-cber-regulated-biologics

48"Vaccine Testing and the Approval Process"https://www.cdc.gov/vaccines/basics/test-approve.html

[159] "Glass along the Value Chain – Case Study | SCHOTT North America," accessed June 30, 2020, https://www.us.schott.com/tubing/english/special_glass/pharma_packaging/glass-along-value-chain.html.

[160] "Glass along the Value Chain – Case Study | SCHOTT North America."

[161] "Glass along the Value Chain – Case Study | SCHOTT North America."

- Presentation of findings to FDA's Vaccines and Related Biological Products Advisory Committee
- External
- (VRBPAC)
- Usability testing of product labeling

After approving a vaccine, FDA continues to oversee its production to ensure continuing safety. Monitoring of the vaccine and of production activities, including periodic facility inspections, must continue as long as the manufacturer holds a license for the vaccine product.

FDA can require a manufacturer submit the results of their own tests for potency, safety, and purity for each vaccine lot. FDA can require each manufacturer submit samples of each vaccine lot for testing.[162] In instances of supply shortages, the FDA will occasionally expedite the lot release process.[163]

Cost. Currently, drugmakers buy vials for less than 11.26 cents apiece.[164] More research is required to determine how to further cut costs to produce vials at scale.

Maintaining the vaccine cold chain
Most vaccines have stringent storage temperature requirements necessary to maintain activity and potency. In some countries, maintenance of the cold chain poses unique challenges usually during distribution by government agencies or local distributors and storage at the place of use. Cold chain deviations can occur not only when temperatures rise above the recommended storage temperature, but for most vaccines it can also occur if the vaccine freezes. Every vaccine comes with experimentally determined guidance on the length of time it can safely be stored above recommended conditions. It is important that vaccines are stored appropriately and monitored at their site of administration, as improper storage could render the vaccine non-immunogenic or potentially harmful.[165] This could present a particular problem in times of emergency, where generally, stricter quality control is needed due to less clinical data, but less clinical data means that there is less knowledge on the exact requirements for the cold chain.

Environmental concerns
Aluminum production includes strip mining for bauxite, an extractive technique that is highly energy intensive and destructive to habitats.[166] While aluminum can normally be recycled to reduce the need for bauxite, more research is required to determine whether lower-purity recycled aluminum can be used for a pharmaceutical vial.

---

[162] "Glass along the Value Chain – Case Study | SCHOTT North America."
[163] Center for Biologics Evaluation and Research, "Lot Release," FDA, March 19, 2020, https://www.fda.gov/vaccines-blood-biologics/biologics-post-market-activities/lot-release.
[164] "Exclusive: Bottlenecks? Glass Vial Makers Prepare for COVID-19 Vaccine," *Reuters*, June 12, 2020, https://uk.reuters.com/article/uk-health-coronavirus-schott-exclusive-idUKKBN23J0TP.
[165] Preiss et al., "Vaccine Provision."
[166] "Malaysia Counts Cost of Bauxite Mining," *BBC News*, January 19, 2016, sec. Asia, https://www.bbc.com/news/world-asia-35340528.

Works Cited

- "Anatomy of a Bottle." Accessed June 4, 2020. https://www.berlinpackaging.com/anatomy-of-a-bottle/.
- "Aptar Pharma QuickStart™ Injectables - Nasal Spray Pumps + Other | Pharma." Accessed July 25, 2020. https://pharma.aptar.com/en-us/dispensing-solutions/aptar-pharma-quickstarttm-injectables.html.
- *Borosilicate Glass Manufacturers, Suppliers, and Industry Information*, 2019. https://www.youtube.com/watch?time_continue=2&v=zz5pCXTDZx0&feature=emb_logo.
- "Bottles and Vials for Pharmaceuticals." Accessed June 5, 2020. https://www.gerresheimer.com/en/products/pharmaceutical-primary-packaging/bottles-vials-made-of-glass.html.
- "Center Hole Cap | Ema Pharmaceuticals, Aluminum Crimp Caps for Pharmaceutical Containers." Accessed June 25, 2020. http://emapharma.com/en/center-hole-cap.
- "CFR - Code of Federal Regulations Title 21." Accessed June 12, 2020. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=211&showFR=1&subpartNode=21:4.0.1.1.11.5.
- DeGrazio, Fran, and Lionel Vedrine. "Quality by Design for Primary Container Components." In *Quality by Design for Biopharmaceutical Drug Product Development*, edited by Feroz Jameel, Susan Hershenson, Mansoor A. Khan, and Sheryl Martin-Moe, 365–401. AAPS Advances in the Pharmaceutical Sciences Series. New York, NY: Springer, 2015. https://doi.org/10.1007/978-1-4939-2316-8_17.
- Encyclopedia Britannica. "Bromine | Properties, Uses, & Facts." Accessed July 1, 2020. https://www.britannica.com/science/bromine.
- Encyclopedia Britannica. "Butyl Rubber | Chemical Compound." Accessed June 12, 2020. https://www.britannica.com/science/butyl-rubber.
- "Exclusive: Bottlenecks? Glass Vial Makers Prepare for COVID-19 Vaccine." *Reuters*, June 12, 2020. https://uk.reuters.com/article/uk-health-coronavirus-schott-exclusive-idUKKBN23J0TP.
- France, Centre. "Industrie Pharmaceutique - A Lailly-En-Val, EMA Pharmaceuticals Travaille Déjà Pour Le Vaccin Anti-Coronavirus." www.larep.fr, June 27, 2020. https://www.larep.fr/lailly-en-val-45740/actualites/a-lailly-en-val-ema-pharmaceuticals-travaille-deja-pour-le-vaccin-anti-coronavirus_13804870/.
- "Glass along the Value Chain – Case Study | SCHOTT North America." Accessed June 30, 2020. https://www.us.schott.com/tubing/english/special_glass/pharma_packaging/glass-along-value-chain.html.
- "Glass Containers for Pharmaceutical Use." Accessed June 5, 2020. http://www.biomed.co.th/english/Article-USP-Chapter660-EP321-Glass-Containers%20for%20PharmaceuticalUse.php.
- "Glass Vials | SCHOTT Pharmaceutical Packaging | SCHOTT North America." Accessed June 5, 2020. https://www.us.schott.com/pharmaceutical_packaging/english/products/vials.html.
- "GuidelinesPackagingPharmaceuticalProductsTRS902Annex9.Pdf." Accessed June 12, 2020. https://www.who.int/medicines/areas/quality_safety/quality_assurance/GuidelinesPackagingPharmaceuticalProductsTRS902Annex9.pdf?ua=1.
- "Here's How To Become A Level Vial Inspector In 2020," May 18, 2020. https://www.zippia.com/level-vial-inspector-jobs/.
- "How Do You Spec a Glass Vial? Infographic Step-by-Step by O.Berk." Accessed June 12, 2020. https://www.oberk.com/packaging-crash-course/infographic-how-to-spec-a-vial.
- "How Pyrex Is Made - Material, Production Process, Manufacture, Making, History, Used, Processing, Components." Accessed July 1, 2020. http://www.madehow.com/Volume-7/Pyrex.html.
- "How to Select Chromatography Vials." Accessed June 12, 2020. http://www.qorpak.com/pages/HowtoSelectChromatographyVials.Janssen, Renaud. "Elastomere Teile Für Parenteralia," 2013, 7.
- "Japan Glass Industry Co., Ltd.: Vial Manufacturing Process." Accessed June 25, 2020. http://www.jgi-jp.com/english/frameset/fset03.htm.
- "LANXESS - Technical Centers - Production Facilities." Accessed July 25, 2020. https://techcenter.lanxess.com/ruc/americas/en/service/12599/uniarticle.jsp?docId=12599.
- "Location | Ema Pharmaceuticals, Aluminum Crimp Caps for Pharmaceutical Containers." Accessed July 25, 2020. http://emapharma.com/en/location.
- "Locations - West Pharma." Accessed July 20, 2020. https://www.westpharma.com/global-locations.

- Lynch, David J., Jeanne Whalen, and Laurie McGinley. “Trump Takes a First Step toward Returning Medical Supply Chains to the U.S.” *Washington Post*. Accessed July 17, 2020. https://www.washingtonpost.com/business/2020/05/19/trump-takes-first-step-toward-returning-medical-supply-chains-us/.
- “Malaysia Counts Cost of Bauxite Mining.” *BBC News*, January 19, 2016, sec. Asia. https://www.bbc.com/news/world-asia-35340528.
- Mathaes, Roman, Hanns-Christian Mahler, Jean-Pierre Buettiker, Holger Roehl, Philippe Lam, Helen Brown, Joerg Luemkemann, et al. “The Pharmaceutical Vial Capping Process: Container Closure Systems, Capping Equipment, Regulatory Framework, and Seal Quality Tests.” *European Journal of Pharmaceutics and Biopharmaceutics: Official Journal of Arbeitsgemeinschaft Fur Pharmazeutische Verfahrenstechnik e.V* 99 (February 2016): 54–64. https://doi.org/10.1016/j.ejpb.2015.11.016.
- Ovadia, Robert, Philippe Lam, Vassia Tegoulia, and Yuh-Fun Maa. “Quantifying the Vial-Capping Process: Reexamination Using Micro-Computed Tomography.” *PDA Journal of Pharmaceutical Science and Technology* 74, no. 2 (March 1, 2020): 171–84. https://doi.org/10.5731/pdajpst.2019.010363.
- “Oxides of Boron, Boric Acids (HS: 281000) Product Trade, Exporters and Importers.” Accessed July 1, 2020. https://oec.world/en/profile/hs92/oxides-of-boron-boric-acids.
- *Pacific Vial Manufacturing - Factory Made*. Accessed June 25, 2020. https://www.youtube.com/watch?v=m7Sfxhrq-9o.
- PIIE. “Trump’s Steel and Aluminum Tariffs Are Cascading out of Control,” February 4, 2020. https://www.piie.com/blogs/trade-and-investment-policy-watch/trumps-steel-and-aluminum-tariffs-are-cascading-out-control.
- “Pharmaceutical Glass Packaging Market | Industry Report, 2019-2025.” Accessed July 24, 2020. https://www.grandviewresearch.com/industry-analysis/pharmaceutical-glass-packaging-market.
- “Pharmaceutical Packaging Market.” Accessed July 20, 2020. https://secure.livechatinc.com/.
- “PP-PET-Solid-Liquid.Pdf.” Accessed June 12, 2020. https://www.gerresheimer.com/uploads/tx_szpdfbook/PP-PET-Solid-Liquid.pdf.
- Preiss, Scott, Nathalie Garçon, Anthony L. Cunningham, Richard Strugnell, and Leonard R. Friedland. “Vaccine Provision: Delivering Sustained & Widespread Use.” *Vaccine* 34, no. 52 (2016): 6665–6671. https://doi.org/10.1016/j.vaccine.2016.10.079.
- Primeau, M. N., N. F. Adkinson, and R. G. Hamilton. “Natural Rubber Pharmaceutical Vial Closures Release Latex Allergens That Produce Skin Reactions.” *The Journal of Allergy and Clinical Immunology* 107, no. 6 (June 2001): 958–62. https://doi.org/10.1067/mai.2001.115630.
- “Production Process.” Accessed June 25, 2020. http://www.aluminum-cap-closure-sheet.com/Production_Process/.
- “Reliance Sibur.” Accessed July 25, 2020. http://www.reliancesibur.com/butyl-rubber.html.
- Research, Center for Biologics Evaluation and. “Lot Release.” FDA, March 19, 2020. https://www.fda.gov/vaccines-blood-biologics/biologics-post-market-activities/lot-release.
- Rowland, Christopher. “A Race Is on to Make Enough Small Glass Vials to Deliver Coronavirus Vaccine around the World.” *Washington Post*. Accessed July 17, 2020. https://www.washingtonpost.com/business/2020/07/13/coronavirus-vaccine-corning-glass/.
- “Royal Rubber - Rubber Supplier.” Accessed July 25, 2020. https://www.royalrubber.com/location.cfm.
- “Silica Sands and Quartz Sands (HS: 250510) Product Trade, Exporters and Importers.” Accessed July 1, 2020. https://oec.world/en/profile/hs92/silica-sands-and-quartz-sands.
- “Stoppers - West Pharma.” Accessed June 12, 2020. https://www.westpharma.com/products/vial-containment-solutions/stoppers.
- “The Glass Bottle Manufacturing Process.” Accessed June 25, 2020. http://www.qorpak.com/pages/glassbottlemanufacturingprocess.
- Thompson, Stuart A. “Opinion | How Long Will a Vaccine Really Take?” *The New York Times*, April 30, 2020, sec. Opinion. https://www.nytimes.com/interactive/2020/04/30/opinion/coronavirus-covid-vaccine.html.
- UACJ Corporation, A major Global Aluminum Group. “Flat Rolling : UACJ Corporation.” Accessed June 27, 2020. https://www.uacj.co.jp/english/techno/production/roll.htm.
- “Vials Forming Lines - Stevanato Group.” Accessed June 12, 2020. https://engineering.stevanatogroup.com/products/glass-processing/vials-forming-lines/.
- “Where We Operate | ExxonMobil Chemical.” Accessed July 25, 2020. https://www.exxonmobilchemical.com/en/exxonmobil-chemical/about-us/where-we-operate.

Supply Chain Visuals


RUBBER STOPPER SUPPLY CHAIN
1
Bromine, isoprene, and isobutylene are sourced for raw materials.
KNOW-LEDGE GAP: SOURCE OF OTHER MATERIALS
KNOWLEDGE GAP: TRANSPORT
Materials are inspected and then combined in a mixer
Mixed rubber is put through an extruder, producing sheets, and then inspected
2
Sheets heated and combined with sulphur for vulcanization
Die-cutter is used to cut and form rubber stoppers
Stoppers washed and dried
Camera inspection and packaging of clean stoppers
3
KNOWLEDGE GAP: WHO/WHERE ARE MAJOR PLAYERS
Stoppers transported to fill and finish facility
Stoppers put onto vials using filling machine
Filled, stoppered, and capped vials packaged and refrigerated for storage and shipment

Team Information

Advisor

Professor Jenik Radon: Jenik Radon is Adjunct Professor at Columbia University, the School of Public and International Affairs, and practices law at Radon Law Offices focusing on international issues. Radon has also been a lecturer at Stanford University's law and business schools, where he taught a class titled access to medicine; and he has been a visiting professor at universities around the world, including in Colombia, Estonia, India and Mexico. For over 25 years, Radon was the attorney for and later an Executor/Trustee of a privately held German pharmaceutical company, Vetter Pharma, the world's leader in the specialized production of pre-filled syringes. For his work Radon has been honored by the republic of Georgia with the Order of Honor, its highest civilian award, and by Estonia with the Order of the Cross Terra Mariana and the Cross of Service. Radon has authored numerous articles and reports, including "*Walk Tall!, A Beautiful Tomorrow for Emerging Nations, An Anthology of Inclusive Principles for National Growth and Prosperity: Equity, Rule of Law and Sustainable Natural Resource Development*," which was published in conjunction with the 2018 APEC conference in Papua New Guinea, and "Climate Action: What Does it Take? Legal Teeth, Not Just Corporate Words" Journal of International Affairs (Columbia University). Radon obtained his B.A. from Columbia University, M.C.P. from the University of California, Berkeley, and J.D. from Stanford Law School. He can be reached at jenik_radon@radonoffices.com.
More information: https://www.sipa.columbia.edu/faculty-research/faculty-directory/jenik-radon.

Team

Dhwani Babla: Dhwani is a Master of Public Health Candidate with a concentration in global health and development at the Mailman School of Public Health at Columbia University. She received her Bachelors in Health Sciences from Simon Fraser University in Vancouver, Canada in 2013 and has lived and worked in several different countries around the globe. In this project, Dhwani provided communication with Indian vaccine companies and focused on understanding some of the gaps in the fill and finish manufacturing process. She can be reached at d.babla@columbia.edu

Gerardo Canto: Gerardo is a Master in International Affairs Candidate specializing in Conflict Resolution at the Columbia School of International and Public Affairs. He obtained his Bachelor of Arts from American University in 2010. Gerardo has a background in international development from his service in the Peace Corps. In this project, Gerardo focused on the vaccine manufacturing process. You can reach him at gc6236a@gmail.com.

Daniel Chan: Daniel is an L.L.M. candidate at Columbia Law School. He obtained his first law degree in Sciences Po, Paris, and have an undergraduate degree in Finance. He specializes in international commercial arbitration and has working experience in both Paris and Hong Kong. In this project, Daniel provided the regulatory overview of the FDA approval process. You can reach him at dhc2144@columbia.edu

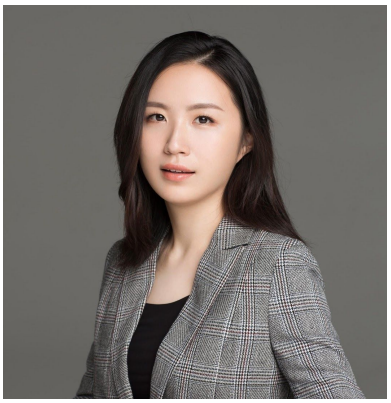
Rebecca Diefenbach: Becca oversees Education and Workforce Development non-profit partnerships and programs at Bloomberg as a member of the Corporate Philanthropy team. She recently completed her Master in Public Administration in Social and Urban Policy at Columbia University's School of International and Public Affairs. She obtained her Bachelor degree in Art History and History at Lehigh University in 2013. In this project, Becca provided communications and public relations support to amplify the message of the capstone project. You can reach her at diefenbach.rebecca@gmail.com.

Dimitrios Fthenakis: Dimitris is an attorney at law and a LL.M. candidate at Columbia Law School. He obtained his first law degree in the University of Athens, Greece, and has a minor degree in Finance. He specializes in corporate finance and M&A transactions, where has working experience as a former trainee lawyer at Deloitte Legal. In this project, Dimitris provided the regulatory overview of the EMA approval process. You can reach him at df2779@columbia.edu.

Yushan (Laria) Lou: Yushan is a Master in Public Administration in Energy and Environment Candidate at Columbia University, the School of International and Public Affairs. She obtained her Bachelor of Science in Business Management from Babson College in 2018. In this project, Yushan focused on identifying the gaps in the fill and finish manufacturing process and finding the regional differences in vaccine production and quality standards between the EU, US and the developing countries' markets. You can reach her at yushan.lou@columbia.edu.

Shannon McKenna: Shannon is a Master in Public Administration in Development Practice Candidate specializing in Conflict Resolution at Columbia University. She obtained her Bachelor of Science from the United States Military Academy in 2009. Shannon has a background in engineering and logistics from her service as a commissioned officer in the United States Army. In this project, Shannon focused on understanding the processes and gaps in the fill and finish manufacturing process, facility development and scalability of anticipated COVID-19 vaccines. You can reach her at mckennasm@gmail.com

Ceri-Lune Renneboog: Ceri-Lune is a Master of Public Health candidate at the Mailman School of Public Health at Columbia University. She obtained a Bachelor of Art in Anthropology and Justice, Peace and Ecology and a Bachelor of Art in International Studies from the University of Alabama at Birmingham in 2018. In this project, Ceri-Lune focused on the limitations of product manufacturing. You can reach her at cr3102@cumc.columbia.edu



Yuexin Zhao: Yuexin is a Master in Public Administration in International Finance and Economic Policy at Columbia University. Yuexin has experience working in the pharmaceutical industry. In this project, Yuexin focused on finding the regional differences, especially the China and India market. You can reach her at yz3579@columbia.edu