MERCK

perspectives on the vaccine industry

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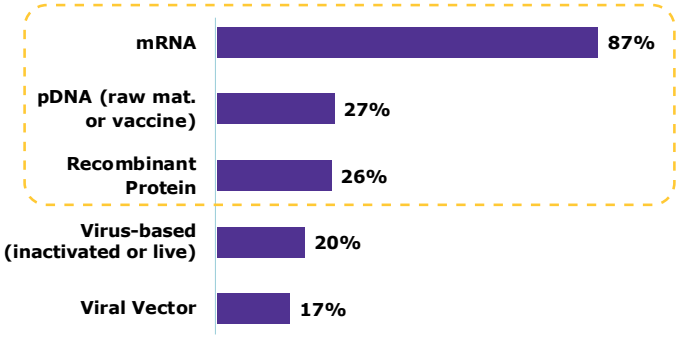
Our organization recently commissioned Economist Intelligence Clearstate, a division of The Economist, to conduct a study on the future of vaccine manufacturing in the Asia Pacific region. Nearly forty industry executives from biopharmaceutical companies, contract development and manufacturing organizations, and research institutes across ten countries were interviewed on topics ranging from the pros and cons of different vaccine modalities to technology adoption and envisioning the facility of the future.

In this whitepaper, we share key findings from the research. Our perspective on the survey findings are offered by Josephine Cheng, one of our senior Process Solutions consultants based in Taiwan.

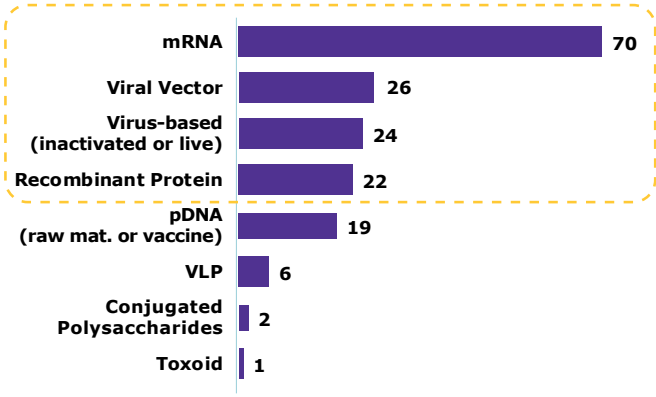
Topic #1: mRNA is a key focus of vaccine manufacturers and is expected to be the dominant modality in the future.

While traditional and modern vaccine modalities will continue to play important roles, **87% of the respondents intend to focus on mRNA** and the majority believe this modality will dominate the future vaccine landscape. Most manufacturers stated an intent to establish capabilities in novel vaccine platforms and indicated that both traditional and modern cell-based vaccines remain important given their proven regulatory record, high efficacy, and generally fewer side effects.

Modalities Producers Intend to Focus on in the Future



Modalities Expected to Dominate Future Market (Weighted Score)



Virus-based (inactivated or live-attenuated vaccines)
pDNA (raw materials for mRNA or vaccines)

When asked whether there remains a role for virus-based vaccines, respondents from large pharma, mid-size pharma and national health research institutes offered differing opinions.

Although mRNA will gain market share, virus-based vaccines still have a role to play

As part of this survey, we asked participants for their views on inactivated vaccines, which is the most dominant vaccine type in the APAC region. We explored whether they think the industry or their organization will move away from inactivated vaccines to newer technologies such as mRNA and viral vector vaccines. Participants' opinions are summarized in table below.

Shift away from inactivated vaccines

Lower efficacy of inactivated vs mRNA
"In the future, protein and mRNA technology platforms will replace the traditional vaccine technology platforms." (Biopharma, CN)

More difficult to produce vs mRNA
"Newer technologies will take over, mRNA vaccines are easier to manufacture, and the efficacy is very good." (Biopharma, IN)

Inactivated lose significance as mRNA and viral vector develops further
"Inactivated vaccines are expected to lose their significance in the coming years. mRNA and viral vector vaccines would continue to grow in the future." (Global Biopharma, JP)

Replaced by mRNA in 10 years
"Inactivated could be replaced, depending on the success of mRNA, perhaps in the next 10 years of development" (Global Biopharma, AU)

Plans already made to replace existing vaccines with mRNA
"We are already putting efforts into our R&D to replace the existing vaccines with mRNA. In the near future, we might use this technology to create other vaccines as well." (Vaccine Manufacturer, ID)

Inactivated will still retain a key role

Proven safety, efficacy, and cost effectiveness (over the long run)
"Inactivated has been safe and effective for years, plus it is cheap, and many companies are in the market already." (Global Biopharma, SG)

Safer with less side effects vs mRNA
"The inactivated COVID vaccine is still the mainstay in mainland China. However, based on the available clinical data, the protection rate is not satisfactory. The traditional process has a longer history of application and although the protection efficiency is lower than that of new technology vaccines, the rate of adverse reactions and side effects is lower." (Biopharma, CN)

"Inactivated vaccines will always be in consideration because of its safe usage, and the technology is also easy to utilize for vaccine production." (State-Owned Biopharma, ID)

Focus on improving existing/mature technology
"We will not consider using mRNA or protein technology to replace traditional production lines for the time being. At present, the traditional production lines in China are mature, and the companies prefer to focus on perfecting the mature products." (Biopharma, CN)

Our Perspective

Given the protection offered by the SARS-CoV-2 mRNA vaccines and the accelerated development timelines, it's no surprise that this modality has gained significant traction and interest across the biopharmaceutical industry. When comparing the development times of different modalities, nucleic acid-based vaccines are the fastest, and as an established platform technology, mRNA enables a tremendous amount of manufacturing flexibility and production speed.

As highlighted in our recent whitepaper on modeling the economics of vaccine manufacturing, mRNA vaccines offer important financial advantages. Our model showed that in routine, large-scale manufacturing, mRNA vaccines would require the least costly capital installation to produce the same amount of target volume. With the same scale, mRNA technology can be used to easily produce many more doses compared to that of an inactivated vaccines production line. These vaccines also require the least facility utilization, thus leaving room for multi-vaccine production.

Survey results indicated that there is continued interest in inactivated vaccines. As such, vaccine manufacturers should remain mindful of related safety concerns including incomplete virus inactivation and the need for a higher facility biosafety level as operators are growing pathogenic viruses during production.

Topic #2: Each vaccine modality, including the highly popular mRNA, offers a range of benefits and challenges.

The survey indicated that mRNA, viral vector, virus-based, and recombinant vaccines are likely to dominate in the future. Survey respondents were asked to describe the benefits and challenges of a range of vaccine modalities. Their feedback is summarized in the table below. A large number of benefits were attributed to mRNA, along with several important challenges, some of which are the result of this being a relatively new modality. These challenges include access to development and production technology and talent and regulatory questions.

Modality	Benefits	Challenges
mRNA	Fast development time Short manufacturing process Flexible and versatile to cover different types of diseases including cancer Lower biosafety levels required Government support Capacity to induce better immune response Proven efficacy (at least for COVID-19) Relatively safe	High development cost High cost of production due to higher consumable costs Navigation of different patents from all over the world Cold storage and transportation cost Limited access to development and production process/technology and talent Question marks over safety levels
Plasmid DNA	Cost-effective Easy to manufacture Can be easily cloned Easy to purify Easy to store and transport High/growing demand	Efficacy (yet to prove long-term effect on immunity) Requires special equipment e.g. gene gun Safety - side-effects not fully discovered
Viral Vector	Easy to manufacture High efficacy Highly templated process Stable	Safety concerns in terms of product stability, consistency, immunogenicity May not be suitable for 2nd or booster dose Require BSL1/BSL2 facility to manage biosafety Lower yield/less cost-effective vs mRNA
Subunit	Easy to manufacture Proven safety, fewer side effects (with approved antigenicity) Proven technology Proven regulatory track record High yield Widely accepted Very stable and easy to store/transport	More failures than hits Complex quality control Require bioinformatic tools Relies on mammalian or bacterial expression which increases the risk of bioburden and adventitious viruses Longer production/purification time

Modality	Benefits	Challenges
VLP	Versatile Less side effects Able to undertake multiple target antigens Proven regulatory track record Can use numerous envelope proteins Proven regulatory track record	Difficult to produce (dealing with multiple subunits and holding structure)
Inactivated	Short development time and easy to scale Safe with very low chance of pathogen reactivation Good efficacy and excellent regulatory track record Very stable Wide access to technology Suitable for long term application	More challenging and costly R&D process Difficult to use (require skilled personnel to perform test during inoculation) Require BSL2/BSL3/BSL4 facility to handle pathogen which means higher facility and manpower cost Require higher safety levels and regulatory approvals Higher dosage (booster) required
Live Attenuated	Higher levels of immunity vs inactivated and subunit vaccines Cost-friendly	Complex manufacturing process required to develop live vaccine Higher biosafety requirements – at least BSL2/BSL3/BSL4 facility – and higher costs to set up Higher manpower cost as it requires trained staff with specific technical knowledge and experience Risk of recovering the virulence and cause disease
Conjugated polysaccharides	High efficacy Cost-effective Safer to use (developed based on bacteria, not virus) High demand with low supply	Long and complex manufacturing process (extraction of polysaccharides, conjugation via chemical reaction, purification, require dedicated suspension plant, challenges in mixing and quality control) Dedicated specificity Low yield
Toxoid	Proven and widely accessible technology Stable Cost effective	Long manufacturing process (detoxification process) Immunogenicity Not versatile

Our Perspective

The survey findings reflect what we know from our customer base – there is active interest in mRNA vaccines, as well as continued application of other vaccine modalities.

A major reason for this is that there has been extensive investment and research into the infection mechanisms used by pathogens which facilitates identification of antigen targets, and of course, a lengthy history of many modalities with regulatory agencies. This has created a foundation for ongoing development based on approaches such as subunit and viral vaccines.

While mRNA vaccines have proven successful against SARS-CoV-2, it will be several years before this becomes a mature modality. The production scale is very impressive, but the production processes, technology, and expertise continue to evolve. Once the mRNA-based regulatory landscape and manufacturing processes are more firmly established, this approach can be used to produce vaccines against new targets (novel variants or new diseases) with a minimal number of process and formulation changes since the majority of the critical quality attributes (CQAs) are the same regardless of the disease target.

Topic #3: Vaccine makers prefer to establish new facilities especially for mRNA, but face technical and regulatory barriers.

More than 60% of survey respondents indicated that they would prefer to establish new facilities or revamp existing facilities with expansion plans over the next few years. Preference for a new facility is driven by the fact that mRNA does not require an extensive setup or that there would be no excess capacity to convert. Other respondents would prefer to update and utilize existing facilities for the pilot phase of development and, in some cases, only establish new facilities after the approval of the vaccine.

For mRNA vaccines, the lack of experience with this modality and the lack of access to technology and manufacturing expertise is a barrier. Similarly, an evolving regulatory environment also presents risk.

We asked, when considering the three newer modalities which are mRNA, viral vector, VLP or protein subunits: do you plan to revamp/replace existing facilities to establish mRNA/viral vector capabilities? Or establish new facilities? Why and what would be the key challenges?

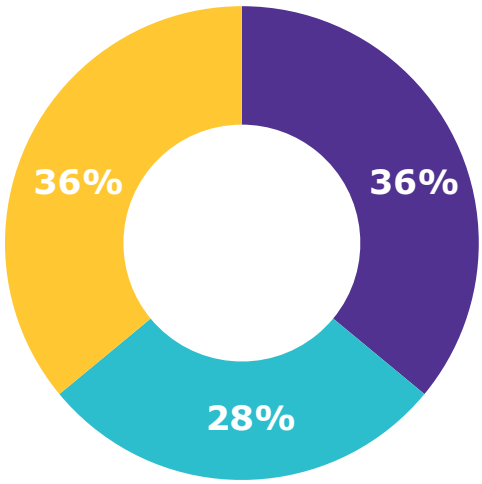
36% Establish New Facilities

Rationales

- mRNA does not require a large setup
- mRNA requires more advanced purification infrastructure & it's easier to set up new single-use facility
- No excess capacity to convert

Challenges

- **Need for experience, access to technology and manufacturing know-how**
- Consumables and raw materials not readily available
- Costly equipment
- Upscaling
- Cold storage
- Funding
- Regulatory approval



28% Revamp Existing Facilities

Rationales

- Prefer to utilize existing facilities for pilot phase and only establish new facilities after trial and approval

36% Neither

Concerns

- **Early stages of exploring mRNA:** Our team is exploring mRNA vaccine development. Once we have adequate knowledge, we can think of a new facility or renovating an existing facility.
- **Regulatory environment still unclear:** As it is a new technology platform in China, it will need to follow the new drug launch process for approval and more comprehensive materials and data will be needed.
- There are risks involved in developing new products and many uncertainties about the future market. Therefore, we do not have a clear timeline and direction at this time.

Our Perspective

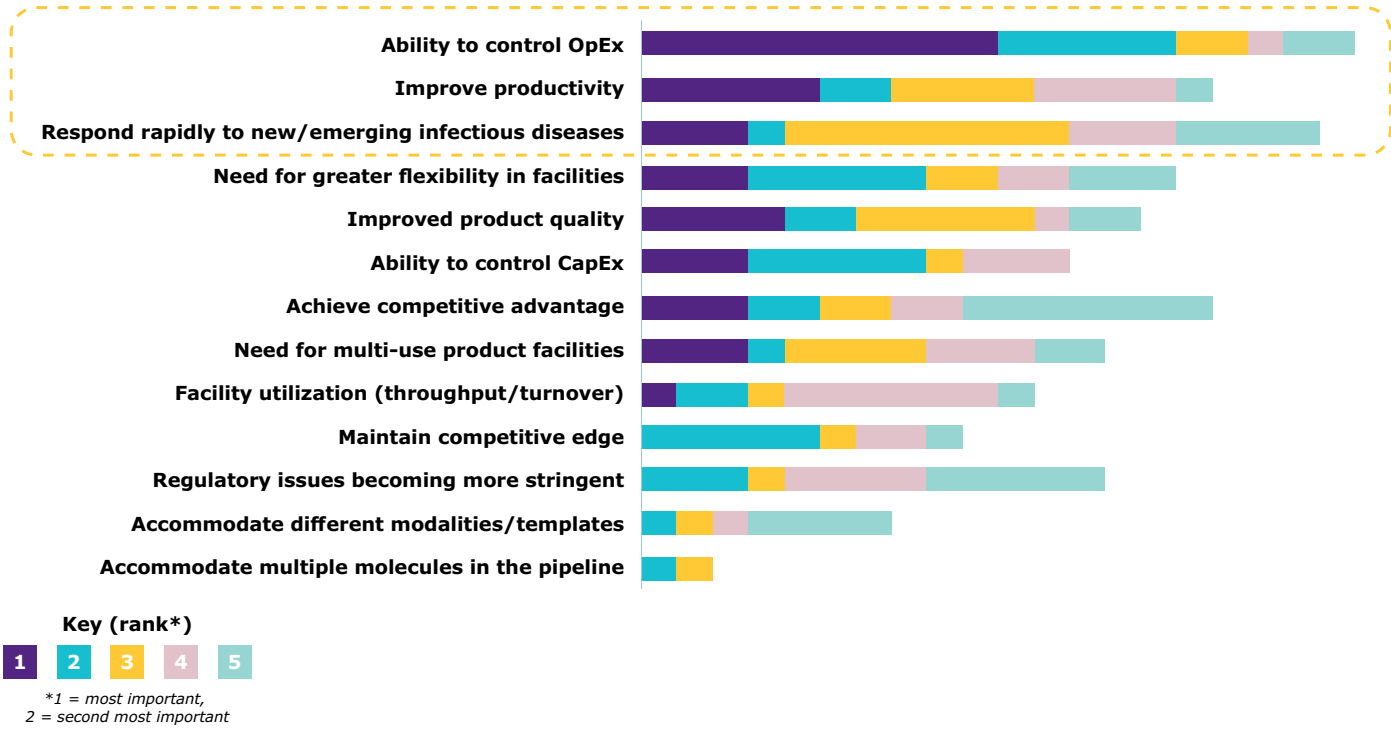
The recent pandemic imparted a sense of urgency across the entire biopharmaceutical industry to develop new vaccines and therapeutics. Given the need to move quickly, revamping existing facilities made the most sense to enable a rapid response. With the pandemic behind us, companies now have time to consider and evaluate a range of options when it comes to vaccine production. With mRNA vaccine production requiring relatively less space than other approaches, new facilities may be more feasible and affordable.

Topic #4: Operating expense, productivity, and the ability to respond rapidly to new disease outbreaks are top motivators for changing technology platforms.

When asked about key considerations and motivations for switching to a different technology platform for vaccine production the top three factors were:

- The ability to control operating expense
- The need to improve productivity
- The ability to respond to new and emerging infectious agents

Key Consideration Factors to Change Technology Platform



Our Perspective

Reponses to this survey questions from APAC participants were similar to those from a previous survey conducted in the EU and North America. One difference is that APAC manufacturers have a stronger focus on improving productivity and operation expenses, while manufacturers in other regions have a stronger focus on remaining competitive and ensuring better and more flexible facility utilization. This finding reflects the fact that major North America and EU pharmaceutical companies developing vaccines are innovation leaders and operating at a larger manufacturing scale.

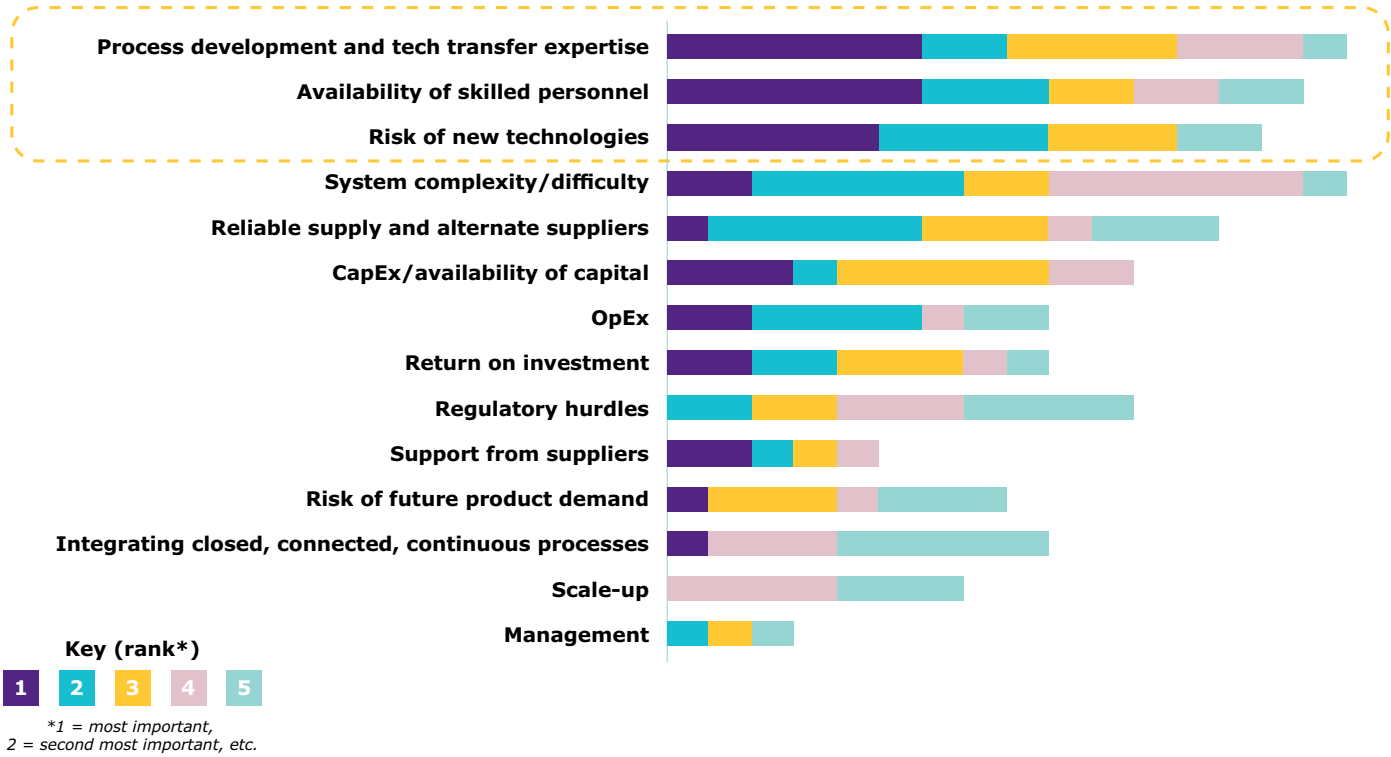
Cost modeling can also be a valuable tool for assisting in the evaluation of operational expenses. For example, use of this cost model indicated that the platform technology and flexibility of mRNA-based vaccines, when manufactured using single-use equipment, require the least capital investment. The smaller production scale reduces the facility

design complexity, and lower utilization rate means that more doses can be produced per batch. As such, this vaccine modality can be a robust starting point for production with low risk.

Topic #5: Key concerns for adoption of new technology are expertise, availability of skilled personnel, associated risks, and the need for a reliable supply chain.

Survey participants were asked to rank their main concerns and challenges when planning for the adoption of new technologies. Availability of expertise, skilled personnel, and the risk of novel technologies were cited as the top concerns. Factors such as the return on investment, anticipated future demand, and scale-up ranked lower on the list of concerns.

Key Concerns for Adoption of New Technology: expertise, availability of skilled personnel and risk of new tech



Our Perspective

Ultimately, selection of which vaccine modality will be produced requires cost considerations and an assessment of available resources. In addition, partnering with a technology provider with global experience in manufacturing all different types of vaccine modalities can further ensure a cost-effective, high-quality process. A strong partner with in-depth expertise and the ability to leverage novel technologies will also help reduce risk and shorten timelines.

Topic #6: The benefits of both modular and hybrid facilities are well-recognized in comparison to a traditional ballroom concept.

We asked: Considering a vaccine manufacturing facility of the future, would you prefer a modular facility or a traditional building with a ballroom concept? Why?

Respondents expressed a preference for either modular manufacturing capabilities or a hybrid approach in comparison to the ballroom concept. Modular facilities are believed to deliver higher efficiency and automation, greater flexibility to produce multiple types of vaccines at the same time, and the ability to respond more rapidly. Hybrid strategies are preferred for the flexibility to accommodate existing and new processes at the same time, and capitalize on the cost effectiveness of traditional manufacturing plus the efficiency and speed of modular facilities.

Hybrid or modular manufacturing facilities are preferred in the future over traditional ballroom concepts

Future vaccine manufacturing facility: Modular vs Traditional vs Hybrid

Traditional

10%

- Lower cost
- More suitable for sub-unit vaccines
- Matches existing expertise and knowledge

Modular

42%

- Automated with higher efficiency
- Ability to respond/change quickly
- Flexibility to produce multiple vaccines at the same time

Hybrid

48%

- Flexibility to accommodate old and new processes
- Capitalize on the benefits of both systems (cost effectiveness of traditional + efficiency/speed of modular)

When asked if they would prefer to receive a fully pre-designed facility with equipment, just the pre-designed facility, or prefer to custom-design and build the facility, with or without equipment, respondents indicated the desire for a modular facility tailored to their specific needs.

Custom-designed modular facilities are most preferred

Future vaccine manufacturing facility:
Custom vs Pre-designed; with or without Equipment

Our Perspective

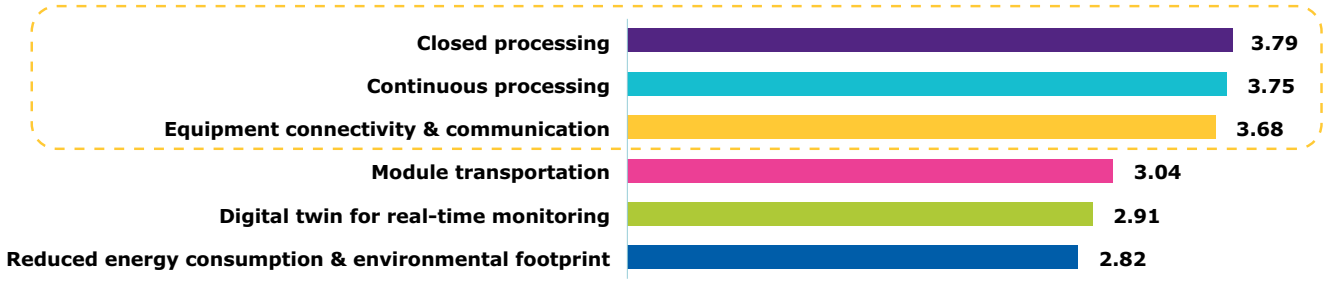
It's clear that the modular concept is appealing for manufacturers, but a hybrid can be a reasonable step towards that ultimate goal. Modular facilities are also appealing as they can enable localized production of vaccines and thus accelerate access to a much larger population. In locations with limited or no infrastructure, a modular approach can be the shortest route to production.

Custom design of a facility – whether modular or traditional – is appealing in that the facility will reflect the exact needs of the organization.

Topic #7: The most important concepts for future vaccine manufacturing facilities are closed and continuous processing, plus equipment connectivity and communication.

When it comes to the vaccine factory of the future, the study revealed that multi-products and custom-designed modular facilities are preferred to enable production of different vaccine and biologics. Closed processing, continuous processing, equipment connectivity and communication are the most important concepts, indicating that quality, safety, productivity, and efficiency remain top priorities.

Future vaccine manufacturing facility: Important Concepts (Average Rating)



*Rate 1 - 5 scale: 5 = most important, 1 = least important

Closed Processing
- Ensure quality and avoid contamination
- Safety

Continuous processing
- Improve productivity
- Lower production cost per unit

Equipment connectivity and communication
- Reduce manpower needs
- Improve efficiency
- Minimize errors

Module transportability
- Flexibility but not valued in China due to regulations restricting production changes or co-locations

Digital twin for real-time monitoring
- Improve efficiency
- Minimize errors

Reduced energy consumption and environmental footprint
- Reduce environmental footprint but not a major concern in vaccine manufacturing currently

Our Perspective

The response to this question demonstrates that the vaccine industry is moving in the same direction as the overall industry – towards a concept of "bioprocessing 4.0" which will be defined by more intensive, more connected, and more highly automated processing. Vaccines are no longer perceived as being quite traditional and using older production technologies. Many vaccine platforms – such as recombinant protein subunits, viral vectors, and mRNA – are becoming quite advanced in their use of technology and moving towards closed and continuous processing, similar to the evolution of monoclonal antibody production.

Going Forward

The COVID-19 pandemic has helped to usher in a new era of vaccines and expanded the roster of modalities that can be applied to address some of our most devastating infectious diseases. The future is bright for this industry and here is what we can anticipate:

- Manufacturers will continue to leverage more modern, leading-edge technologies to develop more advanced vaccine modalities such as mRNA and viral vectors.
- Traditional vaccine types such as inactivated viruses and recombinant protein/subunit will remain an important part of the landscape due to a strong history of investment, efficacy, and regulatory success.
- Most vaccine producers will want the capability to use multiple vaccine templates, producing different biologic modalities in parallel, even if cautiousness is required for entering a new field.
- Vaccine manufacturers are actively planning for expansion and next generation vaccine facilities will undoubtedly incorporate the concepts defined by bioprocessing 4.0.
- A significant barrier is that the manufacturing process will need to be fully digitalized as regulatory authorities rely on data and parameters recorded during production for verification and approval.

Acknowledgment

- Jérome Dalin, Senior Consultant, Bioprocessing Strategy Development, Merck Life Sciences, KGaA, Germany
- EIU Clearstate Project Team

vaccines, empowered

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