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Meeting Report

IABS/CEPI platform technology webinar: Is it possible to reduce the vaccine development time?



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ABSTRACT

The International Alliance for Biological Standardization and the Coalition for Epidemic Preparedness Innovations organized a joint webinar on the use of platform technologies for vaccine development. To tackle new emerging infectious diseases, including SARS-CoV-2, rapid response platforms, using the same basic components as a backbone, yet adaptable for use against different pathogens by inserting new genetic or protein sequences, are essential. Furthermore, it is evident that development of platform technologies needs to continue, due to the emerging variants of SARS-CoV-2. The objective of the meeting was to discuss techniques for platform manufacturing that have been used for COVID-19 vaccine development, with input from regulatory authorities on their experiences with, and expectations of, the platforms.

Industry and regulators have been very successful in cooperating, having completed the whole process from development to licensing at an unprecedented speed. However, we should learn from the experiences, to be able to be even faster when a next pandemic of disease X occurs.

1. Introduction

The International Alliance for Biological Standardization (IABS, <https://www.iabs.org>) and the Coalition for Epidemic Preparedness Innovations (CEPI, <https://cepi.net>) organized a joint webinar on the use of platform technologies for vaccine development. To tackle new

emerging infectious diseases, including SARS-CoV-2, rapid response platforms, using the same basic components as a backbone, yet adaptable for use against different pathogens by inserting new genetic or protein sequences, are essential. New platform technologies such as messenger RNA (mRNA), viral particles, recombinant constructs have significantly contributed to a quick response to the COVID-19 pandemic.

Abbreviation: CEPI, Coalition for Epidemic Preparedness Innovations; CMC, Chemistry, Manufacturing and Controls; CMI, cell-mediated immunity; EMA, European Medicines Agency; FDA, U.S. Food & Drugs Administration; IABS, International Alliance for Biological Standardization; MHRA, Medicines and Healthcare products Regulatory Agency; modRNA, nucleoside-modified mRNA; MPSP, multimeric protein scaffold particles; mRNA, messenger RNA; OMCL, Official Medicines Control Laboratory; PIMF, Platform Master File; saRNA, self-amplifying mRNA; uRNA, uridine RNA; WHO, World Health Organization; ZAPI, Zoonotic Anticipation and Preparedness Initiative.

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The effort to develop vaccines against diseases more rapidly through modern technologies is currently being illustrated by tremendous progress in the speed of development of COVID-19 vaccines. It is also evident that development of platform technologies needs to continue, due to the emerging variants of SARS-CoV-2, something which many vaccine developers are already involved in. Importantly, these developments are not only relevant to the present COVID-19 pandemic but also for future pandemics to come. The aim of the webinar was to discuss techniques for platform manufacturing that have been used for COVID-19 vaccine development, with input from regulatory authorities on their experiences with, and expectations of, the platforms.

1.1. The IMI-ZAPI project – the Platform Master File

Joris Vandeputte, President of IABS, presented the Innovative Medicines Initiative supported Zoonotic Anticipation and Preparedness Initiative One Health Approach strategy to prepare for future pandemics and zoonoses (ZAPI project; IMI Grant Agreement n° 115760, with the assistance and financial support of IMI and the European Commission, and in-kind contributions from EFPIA partners). Efforts were joined within ZAPI to develop a platform technology, called multimeric protein scaffold particles (MPSP). In this scaffold, antigens are “glued in” and the result can be used as a vaccine. Three model viruses were utilized: Middle East Respiratory Syndrome virus, Rift Valley virus (zoonotic) and Schmallenberg virus (potential to become zoonotic). The investigations and research into vaccines and antibodies aimed at being flexible, creating a robust platform and readiness for surge production capacity in case of emergencies. For each of the model viruses, a vaccine prototype was developed. For Middle East Respiratory Syndrome virus and Rift Valley virus, antibody platforms were created. The project also aimed for regulatory innovation. To this end, a Platform Master File (PfMF) has been drafted. A PfMF is part of a licensing dossier intended to speed up the regulatory process, without compromising safety and efficacy. A PfMF avoids repeated discussions of already accepted platforms, and the data collected using those platforms. The goal is thus to enable swift responses to (new) infectious disease threats.

The PfMF is considered a stand-alone part of a marketing authorization and may be common to one or more immunological medicinal products platforms. However, none of the information gathered during PfMF creation may compromise vaccine safety and efficacy although it can be used in emergencies. Safety and efficacy will always need to be demonstrated for the final product.

At present, the PfMF is drafted as part of the new veterinary medicinal regulation in the EU, which will legally be in place from 1st of January 2022. An open question is whether phase III trials can be shortened and simplified if the product is based on a platform. Similarly, can the PfMF be used to adapt existing vaccines to new virus variants.

The PfMF in its current draft form contains a detailed description of the platform expression systems and constructs, a justification of the use of immunogenic epitopes, description of existing regulation that can be used (e.g., all the compliance with material from biological origin), stability (time, constructs, temperatures), and description of compliance with the “3Rs” and total in vitro Quality Assurance and Quality Control for batch release. Importantly, the PfMF constitutes a general framework, while specific requirements have to be determined per product and per platform in annexes to the regulation.

On 18th March 2020, the International Coalition of Medicines Regulatory Authorities wrote that “Opportunities to leverage knowledge accumulated with platform technology should be considered to accelerate the development of a SARS-CoV-2 vaccine manufactured using the same platform”, and that “if a platform technology utilized to manufacture a licensed vaccine or other investigational vaccines is well characterized, it is possible to use toxicology data (e.g., data from repeat dose toxicity studies, biodistribution studies) and clinical data accrued with other products using the same platform to support first-in-human clinical trials for a SARS-CoV-2 vaccine candidate”. This means that

vaccine developers may use the already aggregated platform data and concentrate on the “new” insert instead of redoing the whole process. This principle could be extremely useful with regard to new virus strains.

1.2. Accelerating vaccine development utilizing platform technologies

Adam Hacker, Head of Global Regulatory Affairs at CEPI, expanded on the platform technology progress. Importantly, many of the Regulatory Agencies already have mechanisms in place for accelerating approval under emergency legislation. Hence, the UK Medicines and Healthcare products Regulatory Agency (MHRA) was able to grant the first COVID-19 vaccine emergency approval in the United Kingdom on the 2nd December 2020, the U.S. Food & Drugs Administration (FDA) issued the first emergency approval for the USA on 11th December 2020 and in the EU, the European Medicines Agency (EMA) and the European Commission gave the first COVID-19 vaccine conditional marketing authorization on 21st December 2020. The time from the declaration of the Public Health Emergency of International Concern by the WHO vaccines being licensed across multiple territories was just over 300 days. Nevertheless, in the interim, the pandemic unfortunately evolved, resulting in approximately 70 million confirmed COVID-19 cases and 1.6 million COVID-19 deaths.

What would have happened if vaccine development and approval had been achieved within a hundred days? The shape of the pandemic growth curve would have been different at the point of vaccine approval, and the vaccine might have contributed to preventing an exponential shape. The current regulations and guidelines underpinning vaccine development are not adapted to this environment; the approvals are granted for the vaccines and have afforded limited flexibility to incorporate data across a technology as part of a license review platform. Change has been forthcoming as companies build upon experiences from technologies developed over the years and regulators have applied flexibility, often driven by emergency situations, e.g., the Ebola outbreak in West Africa in 2014, where clinical trial applications were rapidly approved. In June 2020, the US FDA provided the guidance “Development and Licensure of Vaccines to Prevent COVID-19”, informing vaccine developers about what they need to provide and where they can rely on platform experience.

The emergence of new SARS-CoV-2 strains is of great concern but also stimulates a broader conversation to maximize the platform experience and pivot the existing technologies against the new strains. The required amount of data will be reduced; when a vaccine technology is pivoted towards a new virus strain, the same manufacturing process, controls and possibly manufacturing facilities will be utilized, additional preclinical data may not be required, vaccine efficacy studies will not be necessary or limited in size. Moreover, smaller safety databases (less than the typical 3000 subjects) will be acceptable for COVID-19 vaccines against new strains. The European Union is setting up a European bio-defense preparedness plan “HERA Incubator” against COVID-19 variants to bring together researchers, biotech companies, manufacturers, regulators and public authorities to monitor variants, exchange data and cooperate on adapting vaccines. The plan will focus on detecting, analyzing and adapting to virus variants; speeding up regulatory approval of vaccines, providing guidance on data requirements and facilitating the certification of new or repurposed manufacturing infrastructures; and supporting the speedy mass production of adapted or novel COVID-19 vaccines.

CEPI’s ambition is to enable an eco-system between regulators and vaccine developers in order to accelerate the process from identification of the pathogen genomic sequence to approval of a new vaccine. Using the platform experience that companies have accumulated and applying this to vaccine development against new virus strains, it may be possible to achieve development and approval much faster than the 300 days that was achieved for the original COVID strain and a nominal target of 100 days should be in reach. CEPI will partner with developers and

regulators to learn from these experiences and look for further opportunities to streamline and accelerate development with an ambitious target of achieving development and approval against a new pandemic virus in 100 days!

1.3. Can platform technologies enable reduced vaccine development time?

Martin Friede, Coordinator and Lead of the initiative for vaccine research, immunization and vaccines at the World Health Organization, discussed some potential drawbacks with platform technologies. Some issues have previously been encountered: how much does a change in genomic sequence impact the process (to what extent is the process standard)? How do different inserts impact the stability, safety and immunogenicity of the vaccine using the platform? And how does prior exposure to the platform impact safety and immunogenicity?

Introduction of a new sequence into a platform can have a major impact, as was seen in live attenuated influenza vaccines during the H1N1 pandemic. The platform did not readily accept the new insert, which had a different target tissue in the body (trachea) than the old insert (nasal epithelium). Another problem is “repeat immunization hypo-responsiveness” where people who have received the vaccine in previous years have a lower efficacy. This may be caused by an immune response against the common part (e.g., a part of the haemagglutinin stem, which does not provide any neutralizing or beneficial immunity). This is especially important if one platform is intended to be used frequently. Another example of an issue with vaccine platforms: In Australia, inactivation/splitting of the influenza virus had worked well for years, until a certain strain appeared where splitting was no longer complete, leading to inclusion in the vaccine of a small amount of whole virus. The whole virus was completely inactivated, but in young children, residual RNA within the virus triggered a rare but severe adverse event, and the recommendation for children below the age of 9 years was dropped. Finally, a problem with vaccine platforms was encountered in Europe, where flocculates were found in vaccine, because of the introduction of a new virus strain in the vaccine. With new strains, precipitating/aggregating/flocculating occasionally occurs. As it was not known how this would impact safety or immunogenicity, these vaccines were withdrawn from the market.

There are also clinical concerns regarding vaccine platforms. One issue is the potential induction of reactivity/allergy to a component of the vaccine (e.g., polyethylene glycol, dextran), if the platform is used repeatedly and not only within the first year of life – this is currently hypothetical but should be kept in mind. Finally, insertion of certain viral components into the platform may modify cellular tropism, such as a viral glycoprotein which has tropism for neuronal cells, which may lead to infection of the nervous system instead of acting locally in the respiratory tract epithelium, or insertion of virus particles which turn out to have tropism for synovial membranes. Although this is probably only relevant for replicating vectors, the issue with modified tropism impacts safety, which cannot be entirely predicted – so studies are needed each time a new virus (parts) is inserted into this type of platform.

For preparedness, platforms must be ready when they are needed. However, it is not feasible to build vaccine production facilities that are simply waiting for the next pandemic, so what is needed are platforms that are being used on a routine basis and then matched to a pandemic when it occurs. The current COVID-19 pandemic platforms should be introduced in routine use for other vaccines. For example, mRNA platforms could be used for influenza, human papillomavirus (HPV), polio, tuberculosis or human immunodeficiency virus (HIV) vaccines.

Whether the currently existing platforms will be useable for the next outbreak of a disease depends on whether we will better understand the immune responses to the components of the platforms themselves. Finally, it is highly desirable that mucosal platforms are developed, as for many pathogens mucosal immunity might be appropriate and perhaps such vaccines reduce pathogen shedding better than

systemically acting vaccines.

1.4. CureVac's experience with COVID-19 vaccine development

Stefan Mueller, COVID Program Lead at CureVac AG, presented mRNA vaccine development experiences during the COVID-19 pandemic. The mRNA technology rests on three pillars:

Optimized antigen design, optimized mRNA sequence (being different from the antigen design) and optimized delivery system. As to the antigen, the full-length spike (S) protein has proven to have a high efficacy. Introducing variants/mutations into the coding sequence of the mRNA leading to production of the antigen confers only to a minor change of the vaccine's whole mRNA sequence, i.e., more than 99% of the mRNA sequence remains identical from prototype/parental vaccine to variant vaccine. Also, the delivery system remains the same. Would it therefore be enough to perform a Phase I clinical study, comparing the immunogenicity of the sequence changed new vaccine to the original S-sequence to prove that the new vaccine is also efficient? Further, mRNA vaccine manufacturers will continuously improve the mRNA backbone – would all clinical studies need to be repeated or would bridging of immunogenicity and safety knowledge from the existing backbone be sufficient?

Early interaction with regulatory authorities and feedback has been helpful for the development of CVnCoV (CureVac's SARS-CoV-2 mRNA vaccine candidate), e.g., through preparing the necessary data packages. Extrapolation of data from similar vaccines was accepted based on scientific justification. All regulatory agencies have been flexible and responsive, and the review timelines have been accelerated by the authorities. Constructive cross-agency interactions have helped the process. As a drawback, approaching several regulatory authorities increases the risk of receiving diverging answers, which may slow down the process.

In summary, a true platform approach seems possible, and the “plug and play” manner of quickly adapting the S protein sequence should be feasible, to adapt the vaccines and vaccinate the population as soon as possible.

1.5. Project lightspeed – platform examples from a COVID-19 vaccine development

Ruben Rizzi, Director of Global Regulatory Affairs at BioNTech, referred to the International Coalition of Medicines Regulatory Authorities quote from 18 March 2020 ‘Data Requirements Supporting First-in-Human Clinical Trials with SARS-CoV-2 Vaccines’, which provided clear guidance to manufacturers recommending them to consider potential platform technology to accelerate vaccine development. However, the document also raised questions. For example, “vaccine technology platform” has no clear and global regulatory definition. It is clear that not *any* conserved feature shared among different vaccines can be considered a *platform* and manufacturing, nonclinical and clinical implementation aspects are yet to be defined. The regulatory framework needs adaptation to some extent: the manufacturers still think of new vaccines as a unique entity, and not a combination of building blocks. Licensing is applied for the whole product (the vaccine) not the platform. To this end, some lessons should be learned from pandemic influenza vaccines. Moreover, mRNA vaccines, such as the BioNTech/Pfizer COVID-19 vaccine, represent a special form of platform vaccines, which could be used as benchmark for platform approaches because the design and manufacturing processes are agile, reproducible, scalable and predictable.

It's important to note that not all the strategies utilized in the COVID-19 pandemic can be realistically implemented in other situations of less emergency. However, many lessons can be learned from the extremely accelerated processes seen in this pandemic and many common practices can be developed for the future.

BioNTech could use prior experiences with the mRNA platforms to

accelerate their vaccine development, especially during the early clinical phases. They started the first-in-human trial with four clinical vaccine candidates, adding complexity, but also increasing the chance of success. The first human was dosed in April 2020, and only eight months later, the vaccine was approved for emergency use. This was not accomplished by cutting corners but by a combination of hard work, including accelerated review by the regulatory agencies, and the fruitful result of many ideas and principles to try to accelerate each step.

Prior BioNTech experiences from mRNA cancer vaccines were leveraged: as four forms of mRNA (uridine RNA [uRNA], nucleoside-modified mRNA [modRNA], self-amplifying mRNA [saRNA], *trans*-amplifying mRNA) and three different delivery systems (lipoplexes, lipid nanoparticles and polyplexes; protecting against degradation and facilitating entry into the target cells) had been investigated previously. The same ingredients were used for the first four clinical COVID-19 vaccine candidates. All previous clinical trials had been reviewed and approved by authorities, so BioNTech already had experience from authority interactions, including valuable feedback, for example on quality expectations to support early clinical trials. For the COVID-19 vaccine development, an Investigator's Brochure was developed, summarizing all the pre-existing oncology trials with all doses, exposures, formulations and RNA formats together with safety and tolerability data. This is not a strict "platform technology approach" but being able to refer to all these nonclinical and clinical experiences from very similar products, was clearly critical. A platform technology approach was used for the toxicology activities: a toxicology study was conducted for each of the three mRNA platforms (uRNA, modRNA and saRNA), and then the antigen (full-length S protein or receptor-binding domain) effect on the toxicology results was investigated. No antigen-specific effects were observed, and therefore data could be extrapolated to cover all possible combinations and the toxicology program became very flexible to support use of different vaccine candidates in early clinical studies.

The lifecycle management of COVID-19 vaccines is challenging; as the pre-approval phase was very short, it is normal that the post-approval phase will be cumbersome. Many post-approval commitments exist, and data are continuously generated. Additionally, there are many uncertainties related to the biology of the disease: the long-term effects of the disease have to be fully understood yet, and the evolution of the pandemic is uncertain, so that even predictions for the next 12 months are very complicated. Further, the role of the emerging new strains is still unknown, and it is not clear how the "building block" principle of platform technology can be applied to address emerging variants without having to generate new clinical data for every new variant strain.

Establishment of a consistent and long-term adoption of "platform" principles for vaccines will require alignment among all stakeholders and closing of some uncertainty gaps, especially regarding the definitions of medicinal products and new active substances; the understanding of how manufacturing changes to the backbone technology can be handled and managed; the implications for nonclinical and clinical implementation; data protection issues and how to ensure a clear distinction between existing and new products; and whether reporting on platform level or product level is required for pharmacovigilance. Platform technologies will probably become more common in the future, also in non-emergency development, but clear (and updated) definitions and new guidelines are needed to support further evolution of these approaches.

1.6. Round table discussion

Can a fungal platform be faster and cheaper than other platforms, enabling many cheaper and quicker therapeutics?

Joris Vandeputte responded that the ZAPI experience shows that the fungal C1 system is a high-performance system, which can produce high quantities of apparently excellent antigens, in the appropriate conformation, and well glycosylated, which has been confirmed in animal

models. So, this is one of the platforms that should be further explored in the near future.

Are Bayesian statistics inherently better suited for platform approaches than traditional statistical approaches? How can Chemistry, Manufacturing and Controls (CMC) statisticians, knowledgeable in Bayesian methods, be involved to support such initiatives?

Dean Smith responded that Bayesian analyses are increasingly used, facilitated by modern computing. The Bayesian methodology is more suited to deal with multivariate aspects and rapid movement through adaptive clinical trials. It should be applied early in the planning of clinical trials from Phase I on, and can be adapted to elements of CMC but this is not common. Bayesian analyses must be performed by biostatisticians experienced with this methodology, supported by colleagues within the clinical and CMC departments, within a realistic benefit-risk-model.

How to deal with different platform approaches and the complementarity between them, and the need to have different solutions?

Joris Vandeputte responded that having several possible solutions is a good approach. Ruben Rizzi pointed out that relying on different platform approaches is more important from a public health standpoint than from a single developer's standpoint, in order to be best prepared for a next pandemic. Dean Smith added that keeping several platform possibilities open is necessary, as it is not known how the technology responds to novel pathogens, and efforts should not be limited to mRNA technology, even if that is performing well with COVID-19. Having different platforms and investigating different boosting options is very important, especially with upcoming virus variants.

Does the CureVac experience of valuable feedback refer to certain authorities or authorities across different continents?

Stefan Mueller responded that the somewhat diverging responses from authorities mainly stemmed from European agencies and regarded CMC as well clinical and other questions. There was less streamlining than there would have been if all studies had been performed under one agency.

Should self-amplifying RNA be considered to be slightly different or a sub-platform of the standard mRNA platform?

Ruben Rizzi responded that it depends on how the platform is defined in the first place. So far, early clinical data does not show that it has a different clinical profile, but if it is to be brought forward in clinical development, this will be a very relevant question. At this time, there is not a clear definition of what an RNA platform is, and the three RNA technologies are considered separate platforms, as no definition exists that can encompass all of them. Currently, it is not possible to change antigen across the three platforms without generating new data. The same platform has a consistent profile irrespective of the antigen, but the reverse is not true. Stefan Mueller added that there are differences between saRNA and the other mRNAs, and added a follow-up question to regulators: what if the RNA backbone is simply changed slightly so that it is more or less the same but there are some changed characteristics—would it still be the same platform or would it require additional studies and if yes, which?

Flu platforms are more similar to classical vaccines. There are significant differences between the modern platforms currently used for COVID-19 vaccines and those developed within e.g., ZAPI and other initiatives. Even if questions on safety, stability etc. need to be answered, comparison between the systems is critical.

Martin Friede disagreed with flu being similar to anything else. Flu vaccines are so far the only vaccines that a person repeatedly receives (most other vaccines are only given once or twice in life). This makes flu a good example to see how platforms will act when given repeatedly. Furthermore, this is the only platform for which we have experience of its behavior, year after year, with yearly changes of insert.

Certain platforms are permissible and useable across species. Some are already used for routine manufacturing of veterinary vaccines for example, thereby securing continuing technology preparedness and manufacturing capacity. Can we profit from experiences on both sides of

the One Health border?

Martin Friede responded that some of the viral vectors have a completely different safety profile. For example, the VSV vector is considered safe in humans but would be fatal in horses. Joris Vandeputte responded in general: in the veterinary sector, the pox virus recombinants have been used since more than 20 years – for vaccines against more than 20 diseases, in several species. Similarly, the production of cell-based flu vaccines, especially for swine, is a classical approach. The MPSP developed in the ZAPI project is another example, suggesting that experiences from the other side of the One Health border can and should be used. In the COVID-19 discussion, until recently, no specialist knew whether vaccination would prevent circulation of the virus, non-human primate data did already suggest this, but now data from Israel and the UK confirm this.

Can master platform databases be shared with vaccine developers?

Joris Vandeputte explained that the most interesting findings are published in the public domain. More proprietary findings cannot be shared by the regulators, and then it depends on the manufacturers' willingness to share it.

What about Quality Assessment and Quality Control analyses for batch release, such as release assays (e.g., tests of cytopathic effects in cell cultures) which take quite a long time. Today, there are alternatives, faster and more precise, why are these alternatives not yet proposed for regulatory acceptance?

Ralf Wagner responded that all batches of COVID-19 vaccines in Europe have been tested by an official medicines control laboratory (OMCL) that was predefined to make sure that sufficient laboratory capacities are available so that all vaccines can be tested before release on the market, within a very short timeframe. The assays have been established within the respective laboratories during the last half year, i. e., during the licensing procedures. The BioNTech vaccine is currently tested at the Paul-Ehrlich Institute (Germany), the Moderna vaccine is tested in Austria and the AstraZeneca vaccine is tested in the Netherlands. If a company would present a novel assay, e.g., replacing the titration method for viral vector vaccines, this would be welcome and implemented, if possible.

Adam Hacker added that significant advances in assay development and release timelines have been seen within the advanced therapies field, particularly within oncology, where there is significant urgency for the patient to receive the personalized therapy. This way, e.g., sterility assays for batch releases can be performed within 5 days instead of typical 10–12 days previously. Reducing release timelines for vaccines will be important to avoid manufacturing and release bottlenecks. A couple of issues with vaccines need consideration: at the time of the initial phase of roll-out of a new emergency use vaccine onto the market vaccines will have very short shelf life. The standard requirement for additional national batch release testing could mean that the batches expire and are wasted. In order to avoid these bottlenecks, some agencies have begun to allow paper release. The WHO has published a white paper on this procedure. These changes to the regulatory systems are important, both at the time of a pandemic but should also be considered more broadly.

Dean Smith underlined that innovations with lot release assays need to be driven by the vaccine manufacturers – if they can present data that demonstrates that an alternative test is comparable and faster, they should submit this to their agency. With currently authorized COVID-19 vaccines in Canada, to a large extent batch release is granted based on in-house testing performed by the manufacturer. So far, the lead companies have performed this testing satisfactorily under these challenging conditions, and since they are under stringent regulatory control, this has been viewed as an acceptable approach by our agency and by some other stringent regulators. Simultaneously, assays are being established in our lot release laboratories to enhance our insight into these methods.

Joris Vandeputte added that a helpful tool would be to move from batch release testing in animals to *in vitro* testing. Stefan Mueller added that it would be beneficial to have tests that are useable for several

vaccines, e.g., for both BioNTech and CureVac vaccines. That would also increase confidence and reduce discussions back and forth. Ruben Rizzi agreed that harmonization would be desirable, which was impossible so far, due to confidentiality issues and tight timelines.

Ralf Wagner added that it is difficult for an OMCL because each vaccine manufacturer might use specific tests, and might even switch assays during development, even if these assays measure the same parameters. Therefore, in order to prepare for official batch release OMCLs will always implement the assays and standard operating procedures used by the companies as early as possible and alignment is not easy.

Intracellular expression of protein through mRNA platforms emphasizes cell-mediated immune responses but delays the analytical evaluation and release of vaccines. How can vaccines be expedited without losing the importance of cell-mediated immunity (CMI) for efficacy? How can it be done quicker if needed?

Ruben Rizzi responded that one should distinguish between immunogenicity assessment during development and testing for release. CMI is important for the vaccines and data are continuously generated, but this does not have anything to do with batch release, analytical testing (such as integrity and potency assays) and/or timelines.

Marco Cavaleri agreed that CMI is not related to release, but added that irrespective of that, there is still a struggle to understand what role CMI plays for mRNA vaccines; the CMI response might be important for protection along the induced antibodies, and there are differences between Moderna's and BioNTech's CMI response data, e.g., depending on the timing and type of assay used. Data on CMI are therefore very important. Dean Smith agreed that CMI responses are critical and need to be better understood but have no relevance for lot release. There are many important characterization assays on the CMC side, such as *in vitro* translation assays, but they should not be added to the release process, as this would slow it down substantially, with no benefit. It is important to have good analytical tools in Quality Assessment and Quality Control in order to characterize and control these products. The final release testing is important but can be performed by the manufacturers themselves, when production has been demonstrated to be under control. Having a sophisticated CMC understanding of antigen production with a specific platform, as a demonstrated knowledge of the critical quality attributes linked to the clinical performance of their product is essential. Dean Smith urged manufacturers to update their methodologies to allow better characterization of their product and manufacturing processes, particularly for older platforms. Manufacturers should be able to rely on regulators to support innovation based on supportive data with refined manufacturing and test methods. Martin Friede confirmed that old platforms often come along with old assays, which often take a long time to perform, which is undesirable. Unfortunately, efforts to replace these assays have not been fruitful yet and it is necessary for manufacturers to address this and suggest new assays. Ralf Wagner underlined that the assays evaluate the vaccine's compliance with specific quality specifications including potency, and do not say anything about the actual clinical efficacy.

The mRNA platform technology for multivalent vaccines such as flu: is it expected that different mRNA will be competing for their protein expression and presentation, perhaps in the same set of cells? Does this competition for cellular machinery need to be considered?

Ruben Rizzi responded that this must be explored further, but there are experiences from oncological multivalent vaccines expressing different tumor antigens: no such competition issue has been observed. The amount of mRNA from the vaccine is negligible compared to the total amount of cellular RNA. Competition is not expected but needs to be explored.

Stefan Mueller added that there might be a competition if one tries to induce several variants of S protein for biological reasons, but not for translation of RNA. Marco Cavaleri added that EMA would need data on absence or presence of competition. Dean Smith added that while there may not be a molecular competition, there might still be antigen competition, which would have to be evaluated.

What data would the regulators wish to see if a company would develop a bi-, tri- or tetravalent vaccine, containing the old strain and one or several new strains in the same vial, in order to bring the product to the market? This is urgent, since e.g., the South African SARS-CoV-2 strain seems to escape the vaccines.

Steffen Thirstrup assumed that a large clinical study would not be necessary. On the other hand, a multivalent mRNA vaccine must raise relevant immunogenicity and CMI against all the variants. Probably, a study would be requested of subjects vaccinated with the classical strain, to see the immunogenicity against the new strain. The sample size must take into account age variations and other variations. A study in unvaccinated subjects is unrealistic. Marco Cavaleri stated that no field clinical efficacy studies would be required, so the focus would be on immunobridging, probably without correlates of protection, but taking into account a suitable marker, pre-specifying criteria for success. Bridging should be done to show non-inferiority of all strains in the new vaccine in terms of neutralizing antibody titers. An EMA guidance document on this topic, developed after discussions with regulators in other parts of the world, will be released within a short time.

Currently, the human legislation includes an option for vaccine master files, but these are antigen-specific and not applicable to platforms in general. Is such a master file concept under discussion at EMA/European Commission?

Marco Cavaleri explained that discussions are ongoing but not yet final. Hopefully, this can be achieved after the pandemic. We should strive to be more open-minded and flexible in the light of platform technology. Steffen Thirstrup added that it must first be defined what a platform technology is. Then, it is up to the vaccine manufacturers to challenge the regulators and push for a scientific discussion and agreement on what can be done.

What about the transfer of platform technologies to other production sites? What has to be complied with in order to transfer – e.g., to Low- and Middle-Income Countries?

Dean Smith explained that manufacturers in general have good comparability approaches and quality control measures, which could in theory be transferred to any other site with the same or comparable quality management system. It is complicated for manufacturers, but these activities are being undertaken. Ruben Rizzi added that the uncertainties related to any change in manufacturing process, including the addition of production sites, have to be handled moving towards a platform approach – and how a platform is defined, even with some variables changing over time.

What is the panel's opinion on human challenge models?

Marco Cavaleri stated that EMA has always been open to the topic, despite ethical doubts. As stated by the WHO expert group, it should be possible to identify a population in which such studies could be conducted with minimized risk for the participants. EMA has the opinion that such data would deliver important evidence, particularly for vaccines where it is not possible to generate efficacy data through field studies or where efficacy data do not yet exist – e.g., for a completely new platform with a new antigen. It is too early to state whether such studies would be pivotal, but they would definitely generate important evidence. In the UK, such studies are underway. Dean Smith added that such studies could also be used to investigate different routes of vaccine administration and different variant vaccines. Pieter Neels argued that ethics committees and national authorities sometimes block this type of

study. The discussion should be opened up so that more support can be generated, and regulators should also communicate that important evidence could be generated using human infection studies.

Regarding data for mRNA vaccines to be supplied to regulators post-marketing, are there questions on manufacturing, apart from shelf-life studies, or mainly on the clinical part?

Ruben Rizzi answered that the required data package for the BioNTech COVID-19 vaccine was discussed with regulators early in the vaccine development process. In general, once general agreement was reached on the overall principles, requirements and framework, it was a relatively straightforward conversation with the regulators about the required submission package for the emergency/conditional approval and post-authorization commitments. As expected with such a fast development, many post-marketing activities were requested by the regulators. The CMC/overall quality package finally provided was satisfactory and not very different from a normally developed vaccine. No shortcuts were taken. Some additional data needed to be generated, especially clinical and quality data, but this is part of the normal regulatory process.

Marco Cavaleri pointed out that the standards of production are very high, but that the CMC package required under these special circumstances is smaller than normal but considered sufficient. As a compensation, additional post-authorization commitments are made. Dean Smith specified that the focus is on ensuring the consistency of manufacturing. The standards to demonstrate consistency are the same, but the evidence to support it is currently more flexible during the pandemic.

2. Conclusion

Industry and regulators have been very successful in cooperating, having completed the whole process from development to licensing at an unprecedented speed. Having said that, we should learn from the experiences, to be able to be even faster when a next pandemic of disease X occurs.

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Declaration of competing interest

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