



BIONTECH

From Anton to Omicron and Beyond: Towards an mRNA Vaccines Platform

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This slide presentation includes forward-looking statements

This presentation contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, including, but not limited to, statements concerning: BioNTech's expected revenues and net profit related to sales of BioNTech's COVID-19 vaccine, referred to as COMIRNATY® where approved for use under full or conditional marketing authorization, in territories controlled by BioNTech's collaboration partners, particularly for those figures that are derived from preliminary estimates provided by BioNTech's partners; BioNTech's pricing and coverage negotiations with governmental authorities, private health insurers and other third-party payors after BioNTech's initial sales to national governments; the extent to which initial or booster doses of a COVID-19 vaccine continue to be necessary in the future; competition from other COVID-19 vaccines or related to BioNTech's other product candidates, including those with different mechanisms of action and different manufacturing and distribution constraints, on the basis of, among other things, efficacy, cost, convenience of storage and distribution, breadth of approved use, side-effect profile and durability of immune response; the rate and degree of market acceptance of BioNTech's COVID-19 vaccine and, if approved, BioNTech's investigational medicines; the collaboration between BioNTech and Pfizer to develop a COVID-19 vaccine (including a potential booster dose of BNT162b2 and/or a potential booster dose of a variation of BNT162b2 having a modified mRNA sequence); the ability of BNT162b2 to prevent COVID-19 caused by emerging virus variants; BioNTech's ability to identify research opportunities and discover and develop investigational medicines; the initiation, timing, progress, results, and cost of BioNTech's research and development programs and BioNTech's current and future preclinical studies and clinical trials, including statements regarding the timing of initiation and completion of studies or trials and related preparatory work, the period during which the results of the trials will become available and BioNTech's research and development programs; the timing of and BioNTech's ability to obtain and maintain regulatory approval for BioNTech's product candidates; the ability and willingness of BioNTech's third-party collaborators to continue research and development activities relating to BioNTech's development candidates and investigational medicines; the impact of the COVID-19 pandemic on BioNTech's development programs, supply chain, collaborators and financial performance; unforeseen safety issues and claims for personal injury or death arising from the use of BioNTech's COVID-19 vaccine and other products and product candidates developed or manufactured by us; BioNTech's ability to progress BioNTech's Malaria, Tuberculosis and HIV programs, including timing for selecting clinical candidates for these programs and the commencement of a clinical trial, as well as any data readouts; the nature of the collaboration with the African Union and the Africa CDC; the nature and duration of support from WHO, the European Commission and other organizations with establishing infrastructure; the development of sustainable vaccine production and supply solutions on the African continent and the nature and feasibility of these solutions; BioNTech's estimates of research and development revenues, commercial revenues, cost of sales, research and development expenses, sales and marketing expenses, general and administrative expenses, capital expenditures, income taxes, shares outstanding; BioNTech's ability and that of BioNTech's collaborators to commercialize and market BioNTech's product candidates, if approved, including BioNTech's COVID-19 vaccine; BioNTech's ability to manage BioNTech's development and expansion; regulatory developments in the United States and foreign countries; BioNTech's ability to effectively scale BioNTech's production capabilities and manufacture BioNTech's products, including BioNTech's target COVID-19 vaccine production levels, and BioNTech's product candidates; and other factors not known to BioNTech at this time. In some cases, forward-looking statements can be identified by terminology such as "will," "may," "should," "expects," "intends," "plans," "aims," "anticipates," "believes," "estimates," "predicts," "potential," "continue," or the negative of these terms or other comparable terminology, although not all forward-looking statements contain these words. The forward-looking statements in this presentation are neither promises nor guarantees, and you should not place undue reliance on these forward-looking statements because they involve known and unknown risks, uncertainties, and other factors, many of which are beyond BioNTech's control and which could cause actual results to differ materially from those expressed or implied by these forward-looking statements. 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Safety Information

COMIRNATY® ▼ (COVID-19 mRNA Vaccine) has been granted conditional marketing authorisation by the European Medicines Agency to prevent coronavirus disease 2019 (COVID-19) in people from 5 years of age and older. EMA's human medicines committee (CHMP) has completed its rigorous evaluation of COMIRNATY®, concluding by consensus that sufficiently robust data on the quality, safety and efficacy of the vaccine are now available.

IMPORTANT SAFETY INFORMATION

- Do not administer Pfizer-BioNTech COVID-19 Vaccine to individuals with a known hypersensitivity to the active substance or to any of the excipients listed
- Events of anaphylaxis have been reported. Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic reaction following the administration of the vaccine
- There is an increased risk of myocarditis and pericarditis following vaccination with Comirnaty. These conditions can develop within just a few days after vaccination and have primarily occurred within 14 days. They have been observed more often after the second vaccination, and more often in younger males. Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis
- Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions (e.g., dizziness, palpitations, increases in heart rate, alterations in blood pressure, tingling sensations and sweating) may occur in association with the vaccination process itself. It is important that precautions are in place to avoid injury from fainting
- Vaccination should be postponed in individuals suffering from acute severe febrile illness or acute infection. The presence of a minor infection and/or low-grade fever should not delay vaccination.
- As with other intramuscular injections, the vaccine should be given with caution in individuals receiving anticoagulant therapy or those with thrombocytopenia or any coagulation disorder (such as haemophilia) because bleeding or bruising may occur following an intramuscular administration in these individuals
- The efficacy, safety and immunogenicity of the vaccine has not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. The efficacy of COMIRNATY® may be lower in immunosuppressed individuals.
- The duration of protection afforded by the vaccine is unknown as it is still being determined by ongoing clinical trials.
- As with any vaccine, vaccination with COMIRNATY® may not protect all vaccine recipients. Individuals may not be fully protected until 7 days after their second dose of vaccine.
- Comirnaty® has no or negligible influence on the ability to drive and use machines. However, some of side effects mentioned below, may temporarily affect the ability to drive or use machines.
- The overall safety profile of Comirnaty® in participants 5 to 15 years of age was similar to that seen in participants 16 years of age and older.
- The most frequent adverse reactions in children 5 to 11 years of age were injection site pain (>80%), fatigue (>50%), headache (>30%), injection site redness and swelling (>20%), myalgia and chills (>10%).
- The most frequent adverse reactions in adolescents 12 to 15 years of age that received 2 doses were injection site pain (> 90%), fatigue and headache (> 70%), myalgia and chills (> 40%), arthralgia and pyrexia (> 20%).
- In clinical studies, the most frequent adverse reactions in participants 16 years of age and older that received 2 doses were injection site pain (> 80%), fatigue (> 60%), headache (> 50%), myalgia (> 40%), chills (> 30%), arthralgia (> 20%), pyrexia and injection site swelling (> 10%) and were usually mild or moderate in intensity and resolved within a few days after vaccination. A slightly lower frequency of reactogenicity events was associated with greater age.
- In clinical trials, the most frequent adverse reactions in participants 18 to 55 years of age who received a booster were injection site pain (> 80%), fatigue (> 60%), headache (> 40%), myalgia (> 30%), chills and arthralgia (> 20%).
- There is limited experience with use of COMIRNATY® in pregnant women. Administration of COMIRNATY® in pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and foetus.
- It is unknown whether COMIRNATY® is excreted in human milk.
- Interactions with other medicinal products or concomitant administration of COMIRNATY® with other vaccines has not been studied.
- For complete information on the safety of COMIRNATY® always make reference to the approved Summary of Product Characteristics and Package Leaflet available in all the languages of the European Union on the EMA website.

The black equilateral triangle denotes that additional monitoring is required to capture any adverse reactions. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. Side effects can be reported to EudraVigilance [<http://www.adrreports.eu/>] or directly to BioNTech using email medinfo@biontech.de, telephone +49 6131 9084 0, or our website <https://medicalinformation.biontech.de/>

Safety Information

AUTHORIZED USE IN THE U.S.

COMIRNATY® (COVID-19 Vaccine, mRNA) is an FDA-approved COVID-19 vaccine for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 16 years of age and older. It is also authorized under EUA to provide a 2-dose primary series to individuals 5 years of age and older, a third primary series dose to individuals 12 years of age and older who have been determined to have certain kinds of immunocompromise, a single booster dose to individuals 16 years of age and older who have completed a primary series with Pfizer-BioNTech COVID-19 Vaccine or COMIRNATY®, a single booster dose to individuals 18 years of age and older who have completed primary vaccination with a different authorized COVID-19 vaccine. The booster schedule is based on the labeling information of the vaccine used for the primary series.

IMPORTANT SAFETY INFORMATION

Individuals should not get the vaccine if they:

- had a severe allergic reaction after a previous dose of this vaccine
- had a severe allergic reaction to any ingredient of this vaccine

Individuals should tell the vaccination provider about all of their medical conditions, including if they:

- have any allergies
- have had myocarditis (inflammation of the heart muscle) or pericarditis (inflammation of the lining outside the heart)
- have a fever
- have a bleeding disorder or are on a blood thinner
- are immunocompromised or are on a medicine that affects the immune system
- are pregnant, plan to become pregnant, or are breastfeeding
- have received another COVID-19 vaccine
- have ever fainted in association with an injection

The vaccine may not protect everyone. Side effects reported with the vaccine include:

- There is a remote chance that the vaccine could cause a severe allergic reaction
 - o A severe allergic reaction would usually occur within a few minutes to one hour after getting a dose of the vaccine. For this reason, vaccination providers may ask individuals to stay at the place where they received the vaccine for monitoring after vaccination
 - o Signs of a severe allergic reaction can include difficulty breathing, swelling of the face and throat, a fast heartbeat, a bad rash all over the body, dizziness, and weakness
 - o If an individual experiences a severe allergic reaction, they should call 9-1-1 or go to the nearest hospital
- Myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside the heart) have occurred in some people who have received the vaccine. In most of these people, symptoms began within a few days following receipt of the second dose of the vaccine. The chance of having this occur is very low. Individuals should seek medical attention right away if they have any of the following symptoms after receiving the vaccine:
 - o chest pain
 - o shortness of breath
 - o feelings of having a fast-beating, fluttering, or pounding heart
- Additional side effects that have been reported with the vaccine include:
 - o severe allergic reactions; non-severe allergic reactions such as rash, itching, hives, or swelling of the face; myocarditis (inflammation of the heart muscle); pericarditis (inflammation of the lining outside the heart); injection site pain; tiredness; headache; muscle pain; chills; joint pain; fever; injection site swelling; injection site redness; nausea; feeling unwell; swollen lymph nodes (lymphadenopathy); decreased appetite; diarrhea; vomiting; arm pain; fainting in association with injection of the vaccine
- These may not be all the possible side effects of the vaccine. Serious and unexpected side effects may occur. The possible side effects of the vaccine are still being studied in clinical trials. Call the vaccination provider or healthcare provider about bothersome side effects or side effects that do not go away

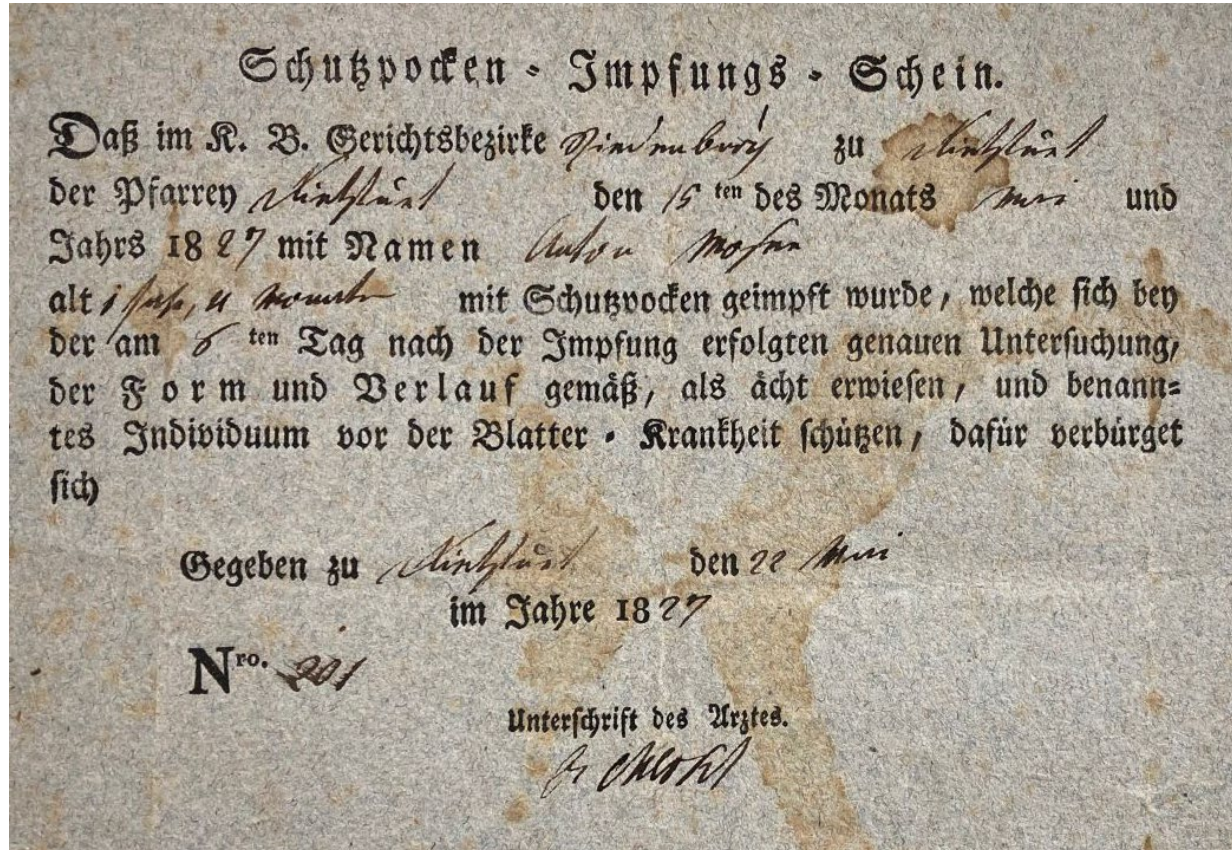
Data on administration of this vaccine at the same time as other vaccines have not yet been submitted to FDA. Individuals considering receiving this vaccine with other vaccines, should discuss their options with their healthcare provider. Patients should always ask their healthcare providers for medical advice about adverse events. Individuals are encouraged to report negative side effects of vaccines to the US Food and Drug Administration (FDA) and the Centers for Disease Control and Prevention (CDC). Visit <https://www.vaers.hhs.gov> or call 1-800-822-7967. In addition, side effects can be reported to Pfizer Inc. at www.pfizersafetyreporting.com or by calling 1-800-438-1985.

Agenda



- Anton - Some history of vaccination
- Current situation of the pandemic
- mRNA manufacturing process overview
- Regulatory aspects regarding introduction of a variant vaccine
 - CMC
 - Nonclinical
 - Clinical
- Outlook

Vaccination Certificate of Anton Moser



private

Protective pox – Vaccination – Certificate

That in the R.(oyal) B.(avarian) judicial district of Riedenburg upon Dietfurt in the parish Dietfurt on the 15th of the month May and the year 1827 with the name Anton Moser, age 1 year, 4 months with protective pox was vaccinated.

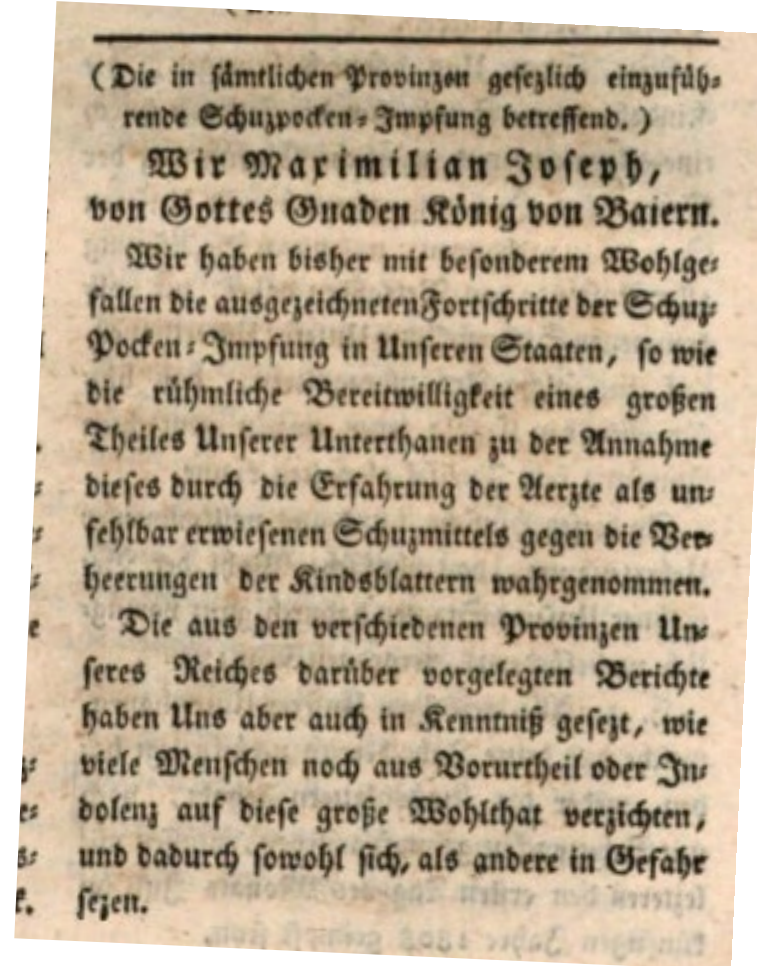
An accurate examination of shape and progress was performed on the 6th day after the vaccination; the named individual is protected from smallpox disease, this warrants

Stated in Dietfurt, Mai 22nd
 In the year 1827

No 201

Signature of the physician
 A. Munk (?)

August 26th 1807, Vaccine mandate in Bavaria



Maximilian Joseph, by the grace of God, King of Bavaria issued a law requiring vaccination against smallpox in 1807.

In the law, He praises the infallibility of the vaccine and the laudable willingness of most people to be vaccinated.

But He also states, that many people abstain from the beneficial vaccination, being it prejudice or indolence, and they do put themselves and others in danger.

Covid-19 pandemic: WHO Coronavirus (COVID-19) Dashboard

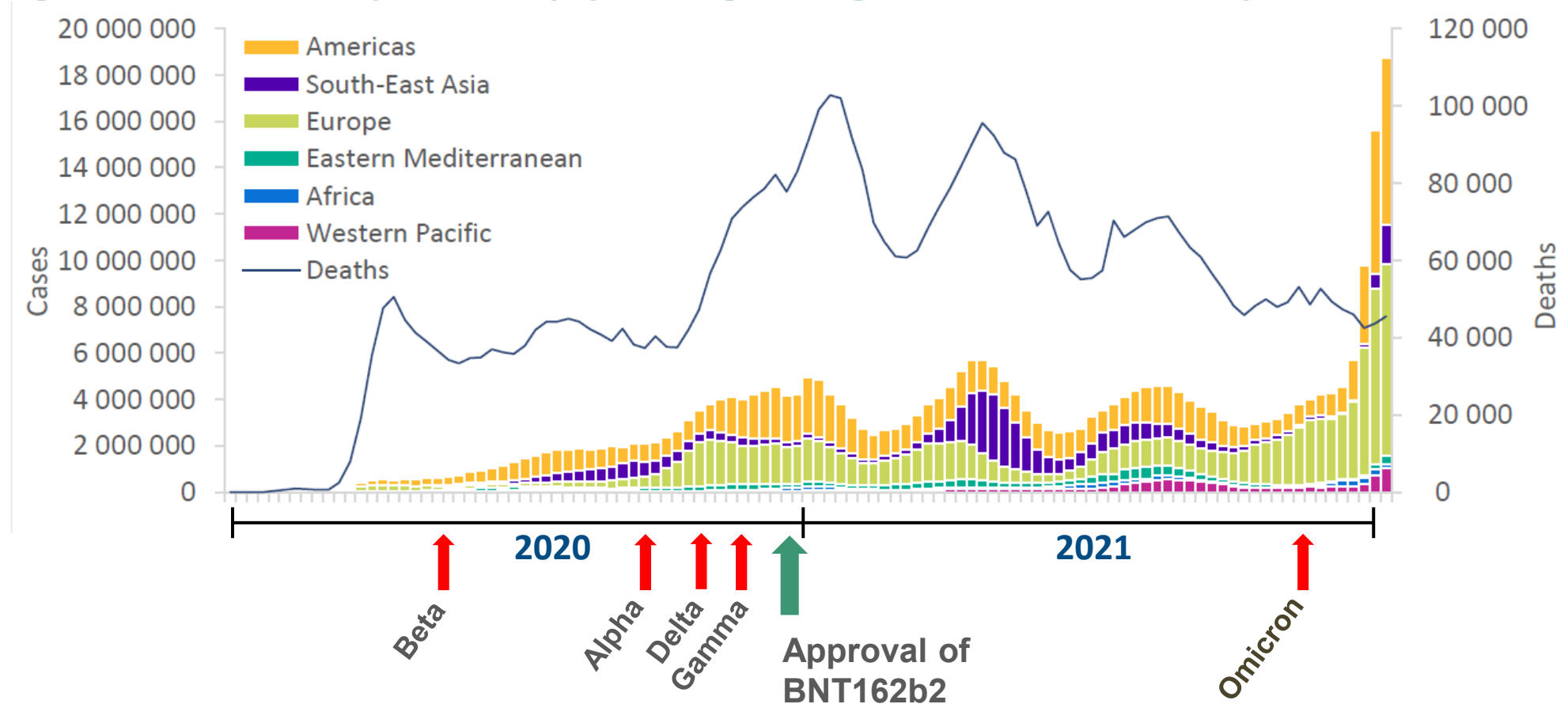
The WHO provides data on the situation of the SARS-CoV-2 pandemic situation.

Cases - cumulative total	⇓	Cases - newly reported in last 7 days	Deaths - cumulative total	Deaths - newly reported in last 7 days
332,617,707		20,037,064	5,551,314	48,573

<https://covid19.who.int/table/> (data shown as of Jan 19th 2022)

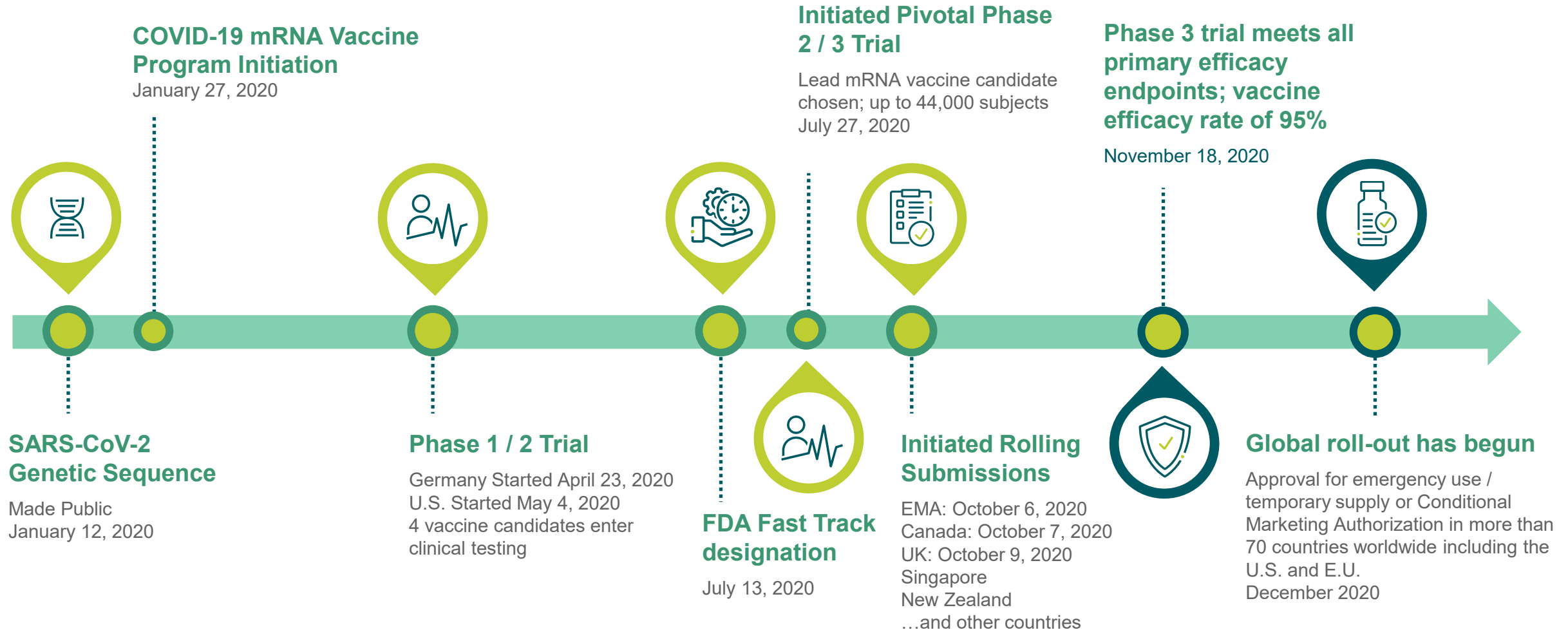
Covid-19 pandemic: Cases and deaths from WHO weekly report (Jan 18th)

Figure 1. COVID-19 cases reported weekly by WHO Region, and global deaths, as of 16 January 2022**



↑ Variants of Concern, earliest documented sample
<https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/> (adapted)

Project Lightspeed – Development and Approval of Comirnat[™]

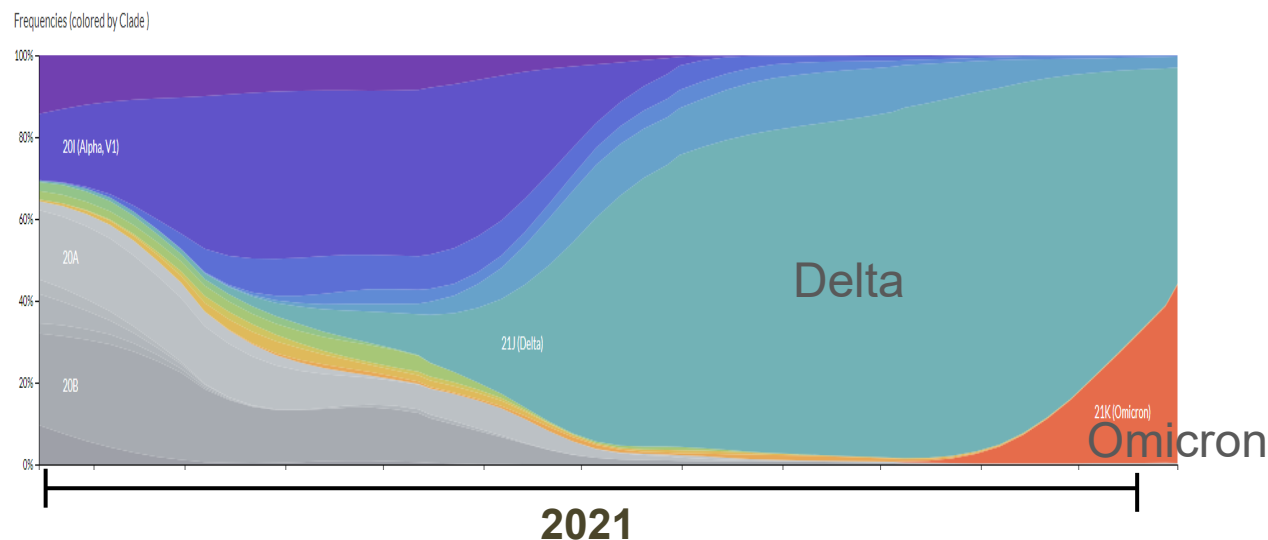


Development of Sars-Cov-2 variants

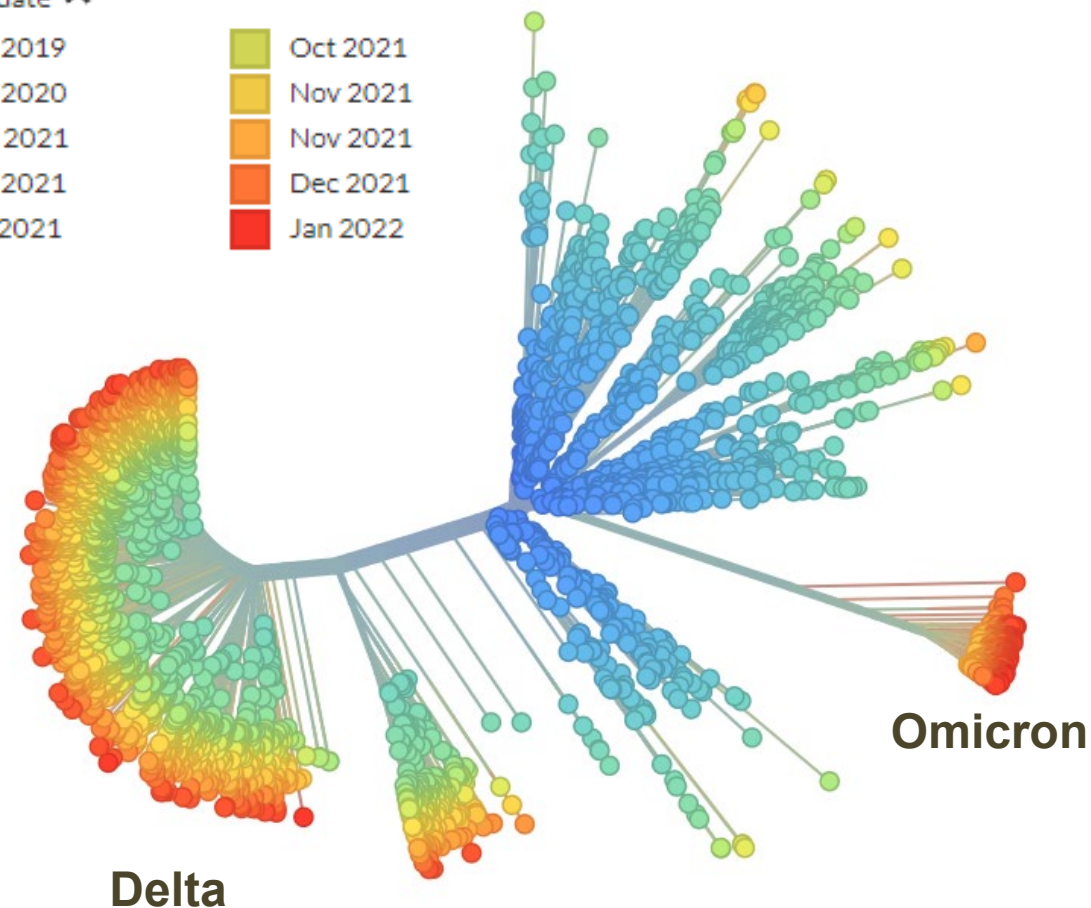
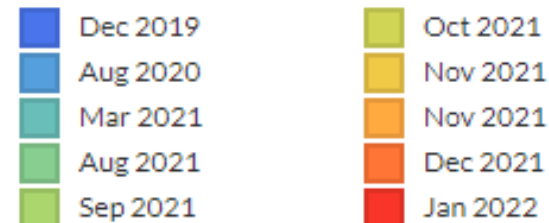
Phylogenetic Analysis shows, that Omicron did not develop out of the Delta variant.*

Frequency of variants

Delta became the predominant variant in Q2 2021.
Omicron was detected first November.



Sampling date ^

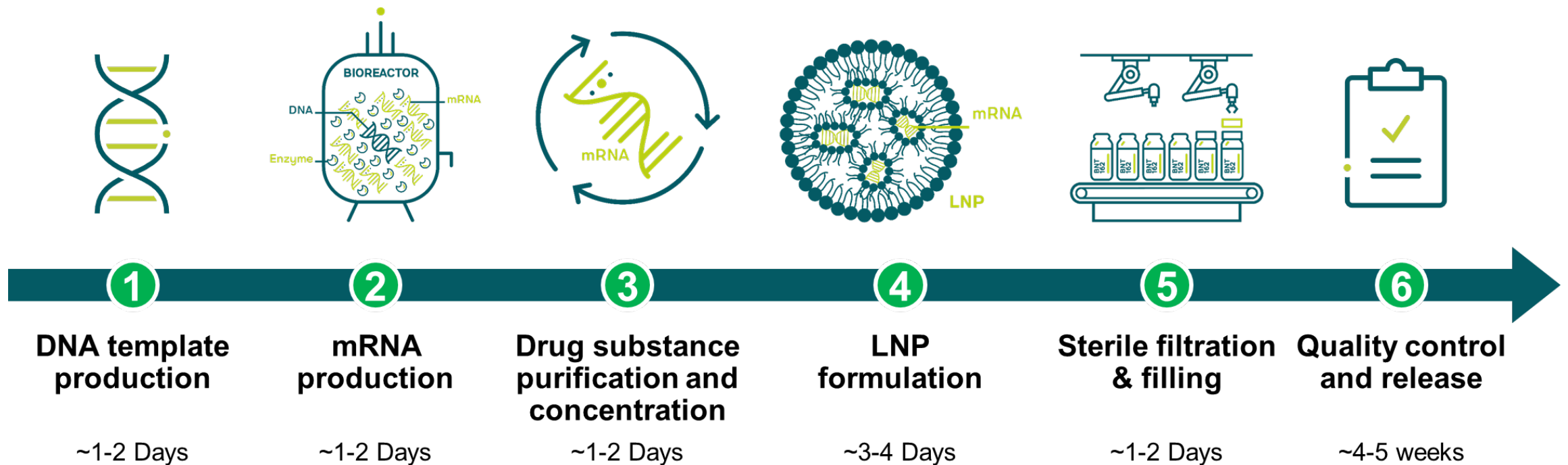


<https://nextstrain.org/ncov/open/global> (adapted)

**“ one process can be used to
manufacture essentially
any mRNA sequence ”**

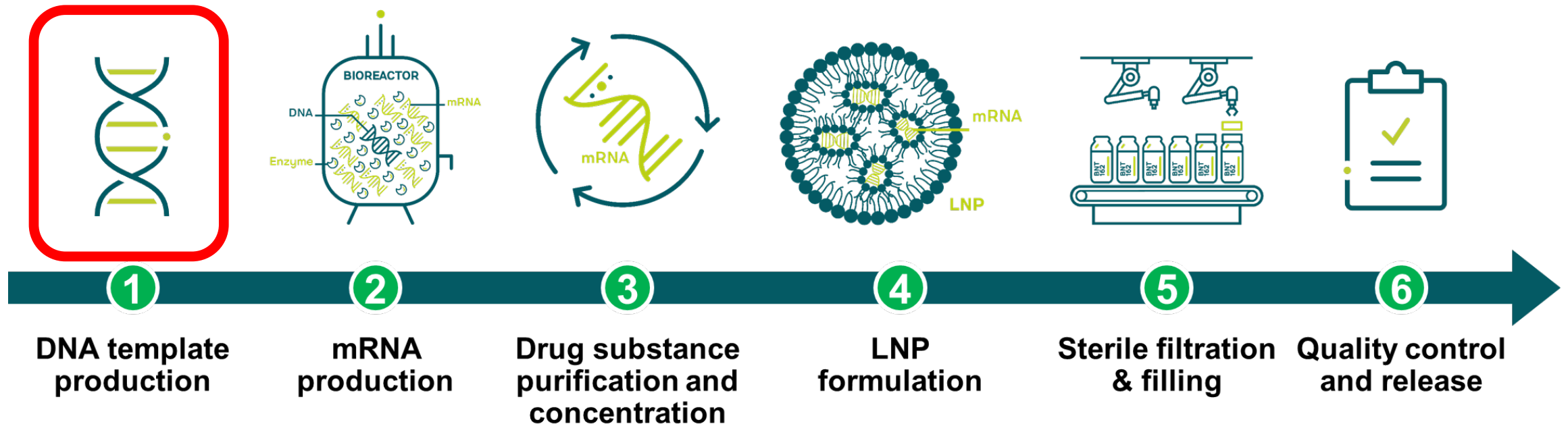
Overview of the mRNA-LNP process

Process overview



Introduction of a vaccine variant (manufacturing process)

Process overview



In addition to the DNA template, the ID test and the potency assay needs to be adapted.

Introduction of a vaccine variant (regulatory aspects)

The EMA and FDA published guidelines on regulatory requirements for vaccines against variant strains of SARS-CoV-2 regarding CMC, nonclinical and clinical evaluation.

EMA:

Reflection paper on the regulatory requirements for vaccines intended to provide protection against variant strain(s) of SARS-CoV-2 (EMA/117973/2021) ¹⁾

FDA:

Emergency Use Authorization for Vaccines to Prevent COVID-19, Guidance for Industry

APPENDIX 2: Evaluation of Vaccines to Address Emerging SARS-CoV-2 Variants

(Version of May 25, 2021) ²⁾

1) https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-regulatory-requirements-vaccines-intended-provide-protection-against-variant_en.pdf

2) <https://www.fda.gov/media/142749/download>

Fundamental requirements



The introduction of a modified vaccine requires an EUA or an MAA and must be manufactured using the same (FDA) or a very similar (EMA) process.

EMA:

“The requirements apply only when both of the following criteria are met:

- The parent vaccine has been granted marketing authorisation in the EU;
- Except for the SARS-CoV-2 antigen(s) to be presented to the human immune system following vaccination, the manufacturing process and controls and the facilities for vaccine production of the variant vaccine, are the same or very similar to those for the parent vaccine.” ¹⁾

FDA:

“The following describes FDA’s current thinking regarding the chemistry, manufacturing, and controls information (CMC), nonclinical data, and clinical data needed to support an amendment to an EUA under section 564 of the FD&C Act (21 U.S.C. 360bbb-3) for a vaccine for the prevention of COVID-19. These recommendations pertain to modified COVID-19 vaccines for the prevention of COVID-19, where the vaccine is made by the same process and manufacturer, but is modified in order to enhance efficacy against COVID-19 caused by a SARS-CoV-2 variant(s).” ²⁾

Justification of the variant vaccine strain



A decision to introduce a vaccine for a virus variant should be discussed with the competent authorities and justified.

Aspects to be taken into account:

- Epidemiological situation
- Urgency
- Relevant recommendations of competent authorities and other organizations (eg WHO)

but also

- Level of protection against the new variant using the original vaccine
- Effects of booster shots of the original vaccine to improve protection against the current strains
- Level of protection of the variant vaccine against current strains in circulation

Introduction of a vaccine variant: CMC/Quality (I)



To be able to file under the existing EUA/MAA, the manufacturing process must be identical or highly similar.

- The FDA requires using the same facilities as used for the original vaccine.
Using the same facilities will reduce the technical risks and avoids an additional tech transfer
- Starting materials must be updated (DNA template for mRNA vaccines)
- Control strategy remains valid (with adaptations possible)
- Manufacturing consistency should be demonstrated

As the manufacturing process of an mRNA vaccine is identical for both, the original vaccine and the variant vaccine, the technology is well suited to react quickly to emerging Variants of Concern.

Introduction of a vaccine variant: CMC/Quality (II)



For mRNA vaccines, the introduction of a different DNA requires changes in analytical assays.

- Testing of critical quality attributes should be performed. Changes (identity, potency) requires adequate scientific and/or clinical justification.

The identity test should be able to distinguish between the two vaccine variants. However, as the initial identity test might not have been developed to differentiate between variants, this might trigger some additional considerations.

- According to the EMA, the registered shelf life would be applicable. Confirmation of the shelf life using available data (real-time or accelerated) is required as well as confirmatory real-time stability data need to be provided post-approval.

The FDA also requests stability data, but no details are given in the guideline.

Introduction of a vaccine variant (nonclinical)



The EMA does not require any further in-vitro or in-vivo nonclinical testing. Any data submitted will be viewed as supportive.

For the FDA, a list of nonclinical studies of the original SARS-CoV-2 vaccine should be provided. These data should have been obtained using the same manufacturer and process.

In general, the FDA states, that for a variant vaccine additional studies may not be warranted.

Nevertheless, the FDA encourages to perform challenge studies using both vaccines, but these studies are not required to start the clinical studies.

Introduction of a vaccine variant (clinical)



The variant vaccine might be used as

- A primary vaccination in subjects, naive to infection or vaccination with the original vaccine.
- As a (single) dose given to subjects who previously received primary vaccination with the original vaccine.
- A vaccination in subjects, who had a SARS-CoV-2 infection.

The EMA expects data from at least one clinical study in naive subjects with the submission.

The FDA suggests to perform studies in both populations.

The clinical studies should compare the immune response of the original vaccine and the variant vaccine.

Introduction of a vaccine variant (clinical)



The clinical strategy should also consider, if

- The variant vaccine is intended to replace the original vaccine on the market.
- The original strain is still in circulation (EMA) ¹⁾
(This statement requires some interpretation).

Both agencies consider phase III efficacy studies as not required for the introduction of a variant vaccine.

The current guidelines provide a balance between data needed on safety and efficacy and, on the hand an approach to allow a fast reaction in case needed.

Both agencies state in the guidelines, that the epidemiological situation might justify alternative approaches and that the requirements could be adapted.

The manufacturer's perspective



The introduction of a vaccine for a variant of concern must be carefully considered.

- Degree of protection of the population by the original vaccine (including booster shot).
Based on available data (not shown), protection against Delta was considered sufficient.
- Additional resources for variant vaccine development and manufacturing needed.
- Impact on overall manufacturing capacity (running at full capacity).
- Added complexity with respect to GMP compliance and the supply chain due to having two products in the market.
- Parent strain might still in circulation.
- New variants will appear.

BioNTech/Pfizer have decided to start the development of a vaccine against the Omicron variant.

Status and Outlook



The development of Comirnaty™ was an unprecedented example in collaboration of scientists, development, operations with partner companies.

In 2021, BioNTech/Pfizer manufactured more than 3 billion doses of Comirnaty™.

If needed, we will adapt the our mRNA vaccine to SARS-CoV-2 Variants of Concern.

In addition to provide highly efficient vaccines to fight the COVID-19 pandemic, we aim to use the mRNA technology in the development of vaccines for other infectious diseases such as tuberculosis and malaria.

Acknowledgements

- Ugur Sahin and the BioNTech Board
- BioNTech team
- Our partners in the COVID-19 program



- All partner companies for extraordinary support



Thank you very much!