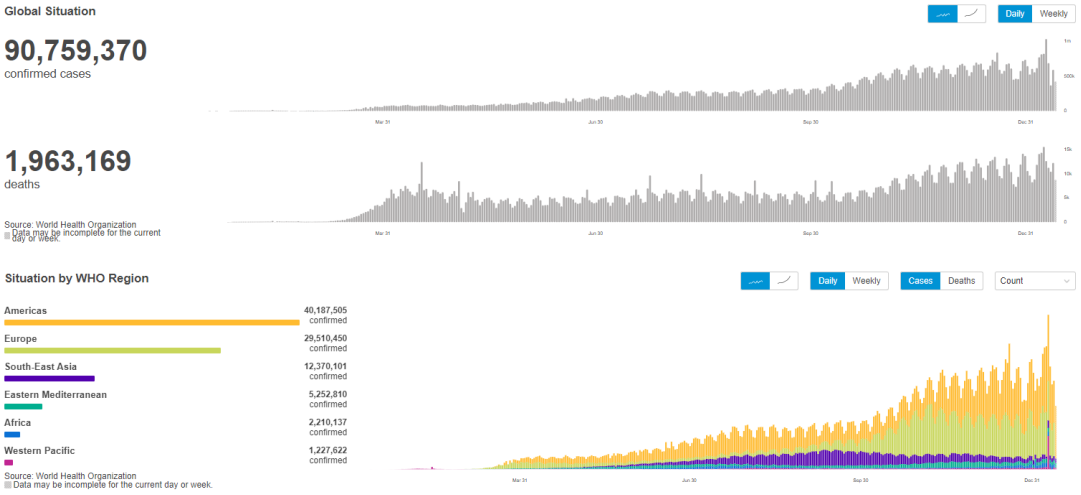
Regulatory Update Q4 2020 - Special Topic

Regulatory Considerations and Flexibility for COVID-19 Drug Development

COVID-19 Background

On January 30, 2020, the World Health Organization (WHO) declared the outbreak a public health emergency of international concern. On March 11, 2020, WHO characterized COVID-19 as a pandemic. Globally, as of January 14, 2021, there have been over 90 million confirmed cases of COVID-19, including over 1.9 million deaths, reported to WHO (Figure 1).

Figure 1. Confirmed Cases Reported to WHO



Regulatory Considerations and Flexibility

The regulatory authorities are contributing to global efforts to save lives during the COVID-19 pandemic by expediting the development and approval of safe and effective treatments and vaccines, supporting the continued availability of medicines, and providing reliable information to patients and healthcare professionals.

FDA

The FDA is committed to providing timely recommendations, regulatory information, guidance, and technical assistance necessary to support rapid COVID-19 response efforts. The Coronavirus Treatment Acceleration Program (CTAP) uses every available method to move new treatments to patients as quickly as possible, while at the same time finding out whether they are helpful or harmful. In addition, guidance documents related, but not limited to, regulatory advice, drug development, manufacturing, GMP considerations, and regulatory inspections are in place to facilitate the development and ensure the safety, effectiveness, and quality of COVID-19 treatments and vaccines.

As of December 31, 2020, the U.S. FDA approved one antiviral drug, Veklury (Remdesivir) for COVID-19 treatment, and issued Emergency Use Authorization (EUA) for COVID-19 vaccine Pfizer-BioNTech COVID-19 vaccine, manufactured by Pfizer and BioNTech, and COVID-19 vaccine manufactured by ModernaTX, Inc. The FDA also authorized EUAs for monoclonal antibodies being used for COVID-19 treatments, including one for bamlanivimab manufactured by Eli Lilly. The other EUA is for casirivimab and imdevimab (administered together), manufactured by Regeneron Pharmaceutical. Bamlanivimab, casirivimab and imdevimab are all recombinant neutralizing human IgG1 monoclonal antibodies that target the receptor-binding domain of the SARS-CoV-2 spike protein. All five products are investigational drugs and are not currently approved for any indication. The FDA expects manufacturers whose COVID-19 treatments or vaccines are authorized under an EUA to continue their clinical trials to obtain additional safety and effectiveness information and pursue licensure.

Key updates are listed as follows:

- Notice to Stakeholders: Questions and Answers on Regulatory Expectations for Medicinal Products for Human Use During the COVID-19 Pandemic (April 2020)
- COVID-19 Public Health Emergency: General Considerations for Pre-IND Meeting Requests for COVID-19 Related Drugs and Biological Products (May 2020)
- Effects of the COVID-19 Public Health Emergency on Formal Meetings and User Fee Applications - Questions and Answers (May 2020)
- Development and Licensure of Vaccines to Prevent COVID-19 (June 2020)
- Good Manufacturing Practice Considerations for Responding to COVID-19 Infection in Employees in Drug and Biological Products Manufacturing (June 2020)
- Resuming Normal Drug and Biologics Manufacturing Operations During the COVID-19 Public Health Emergency (September 2020)
- The FDA's Vaccines and Related Biological Products Advisory Committee and its Role in Advising the Agency on COVID-19 Vaccines (October 2020)
- Emergency Use Authorization Update - Drug and Biological Products (December 2020)
- Guidance Documents Related to Coronavirus Disease 2019 (COVID-19); Availability (December 2020)

EMA

The EMA is interacting with developers of potential COVID-19 treatments and vaccines to enable promising medicines to reach patients as soon as possible. The EMA also provides guidance to help speed up medicine and vaccine development and approval for COVID-19, and on how they should address the regulatory challenges arising from the COVID-19 pandemic. The EMA established COVID-19 EMA pandemic task force (COVID-ETF) to take quick and coordinated regulatory action related to COVID-19 medicines.

EMA's CHMP has authorized the use of a medicine to treat COVID-19, and two COVID-19 vaccines under Conditional Marketing Authorization. Veklury (Remdesivir), an antiviral medicine manufactured by Gilead Sciences Ireland UC, is the first COVID-19 treatment recommended for EU authorization. On December 21, 2020, Comirnaty, developed by Pfizer-BioNTech, was authorized as the first vaccine in the EU, and the COVID-19 Vaccine Moderna is authorized as the second. The regulatory process for the evaluation and approval of vaccines recommended by EMA is shown in Figure 2. Figure 3 details how EMA speeds up the vaccine development and approval for COVID-19.

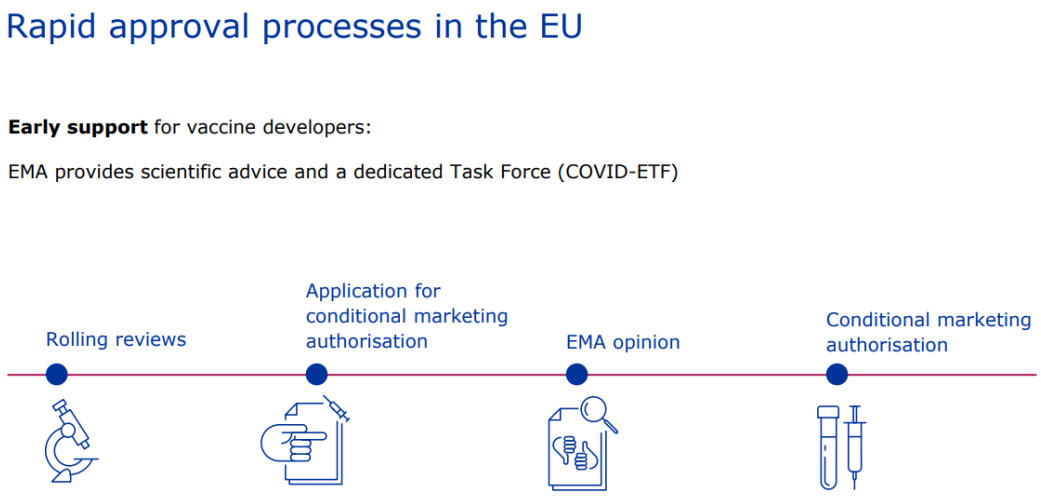


Figure 2. Regulatory Process for the Evaluation and Approval of Vaccines Recommended by EMA

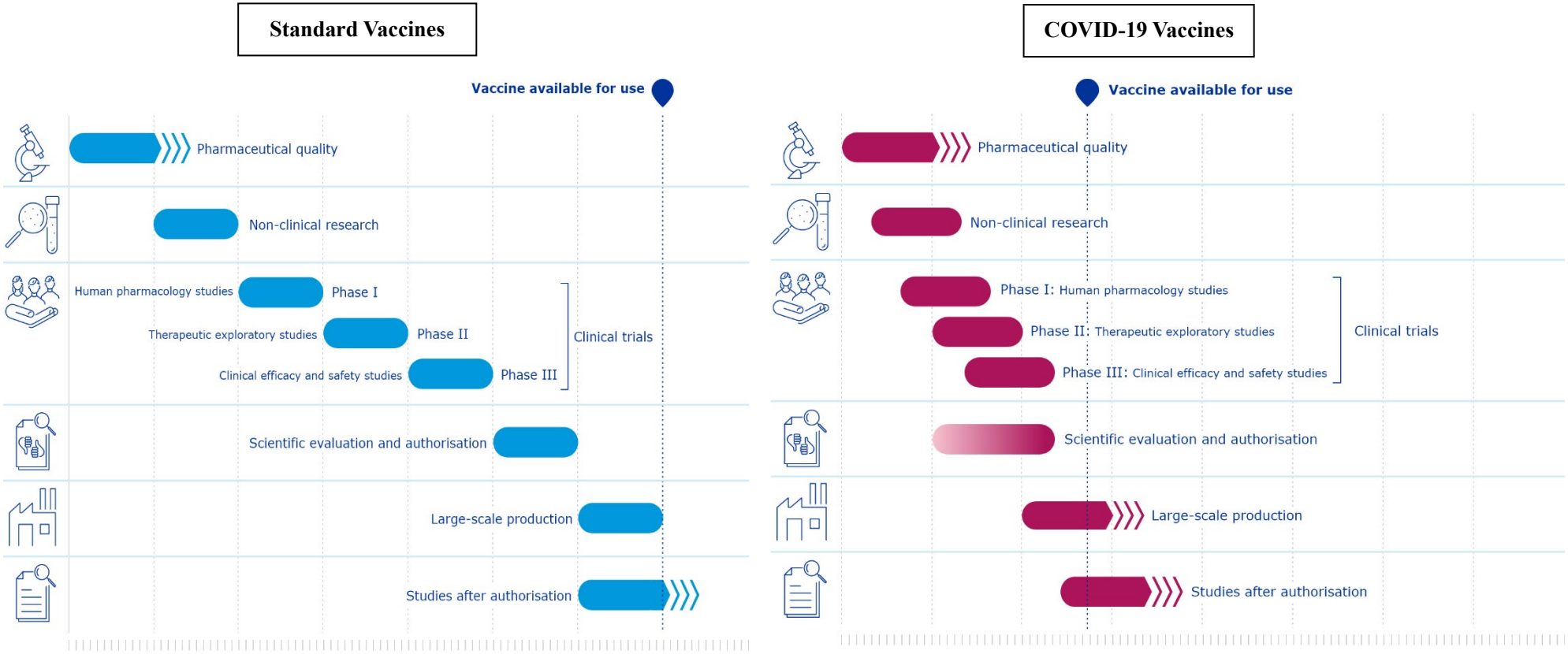


Figure 3: Indicative Timelines for COVID-19 Vaccines Compared with Standard Vaccines

Key updates are listed as follows:

- EMA Establishes Task Force to Take Quick and Coordinated Regulatory Action Related to COVID-19 Medicines (April 2020)
- COVID-19: How EMA Fast-Tracks Development Support and Approval of Medicines and Vaccines (May 2020)
- EDQM Provides COVID-19 Vaccine Developers with Free Access to Quality Standards Applicable in Europe (June 2020)
- Questions and Answers on Regulatory Expectations for Medicinal Products for Human Use During the COVID-19 Pandemic (Updated: July 2020)
- HMA/EMA Statement on Approval of Vaccines (November 2020)
- Guidance for Medicine Developers and Other Stakeholders on COVID-19 (Updated: December 2020)
- Treatments and Vaccines for COVID-19: Authorized Medicines (Updated: December 2020)

Agency Collaboration

During the COVID-19 pandemic, the FDA has been working with the EU and its EMA to strengthen medical products cooperation, including issues related to COVID-19. The FDA and the EU are also promoting engagement with global regulators under the International Coalition of Medicines Regulatory Authorities (ICMRA) forum, comprised of 28 regulatory authorities from around the globe. The ICMRA supports strategic coordination and international cooperation among global medicine regulatory authorities. The ICMRA members have stepped up global collaboration to facilitate and expedite the development and evaluation of COVID-19 treatments and vaccines.

Key updates are listed as follows:

- Global Regulatory Workshop on COVID-19 Vaccine Development (March 2020)
- ICMRA Statement on COVID-19: International Regulators Pledge Collective Support to Combat COVID-19 (April 2020)
- Global Regulators Work Towards Alignment on Policy Approaches and Regulatory Flexibility During COVID-19 (June 2020)
- Partnering with the European Union and Global Regulators on COVID-19 (June 2020)
- FDA Holds Meetings with EC and EMA to Strengthen Medical Products Cooperation (June 2020)
- WHO-ICMRA Joint Statement on the Need for Improved Global Regulatory Alignment on COVID-19 Medicines and Vaccines (November 2020)
- Statement on Continuation of Vaccine Trials (December 2020)

Part 2: Regulatory Inspections during COVID-19

U.S. FDA

Due to the COVID-19 pandemic, the FDA announced in March 2020 that it was temporarily postponing all domestic and foreign routine surveillance facility inspections.

With respect to pre-approval inspections, the FDA intends to continue using other tools and approaches where possible, including requesting existing inspection reports from other trusted foreign regulatory partners through mutual recognition and confidentiality agreements, requesting information from applicants, and requesting records and other information directly from facilities and other inspected entities.

In response to the suspension of assignments during the public health emergency, beginning the week of July 20, 2020, the FDA began to work toward resuming prioritized domestic inspections. Either the FDA is continuing to conduct only "mission-critical" inspections on a case-by-case basis or, where possible to do so safely, resuming prioritized domestic inspections based on the determination of its COVID-19 Advisory Rating system, which generally include pre-approval and surveillance inspections. Foreign pre-approval and for-cause inspections not deemed mission-critical remain temporarily postponed. Factors to define "mission-critical" inspection include, but are not limited to, whether the products have received Breakthrough Therapy (BT) designation or Regenerative Medicine Advanced Therapy (RMAT) designation.

For applications that the FDA determines that an inspection is needed before the approval, the FDA will communicate this to the applicant by either issuing a complete response letter or by deferring action on the application. However, sponsors will not automatically receive a complete response letter if the FDA cannot conduct an inspection.

In December 2020, the FDA issued another guidance titled *Review Timelines for Applicant Responses to Complete Response Letters When a Facility Assessment Is Needed During the COVID-19 Public Health Emergency*. The FDA says that resubmission of 351(a) BLA under PHS Act will be Class 2 timeline of 6 months, consistent with existing policies when a facility inspection or alternative tools for facility assessment are required. Application types that will stick to existing user fee timelines include, but not limited to, resubmission of original 351(k) biosimilar BLAs under PHS Act (6 months) and manufacturing supplements (4 months) and resubmission of manufacturing supplement of 351(a) BLA under PHS Act (4 months).

Key updates are listed as follows:

- Coronavirus Update: FDA Steps to Ensure Quality of Foreign Products (February

2020)

- Coronavirus (COVID-19) Update: FDA Focuses on Safety of Regulated Products While Scaling Back Domestic Inspections (March 2020)
- Coronavirus Disease 2019 (COVID-19) Update: Foreign Inspections (March 2020)
- Coronavirus (COVID-19) Update: FDA Updates on Surveillance Inspections during COVID-19 (May 2020)
- COVID-19 and Beyond: Oversight of the FDA's Foreign Drug Manufacturing Inspection Process (June 2020)
- Coronavirus (COVID-19) Update: FDA Prepares for Resumption of Domestic Inspections with New Risk Assessment System (July 2020)
- Manufacturing, Supply Chain, and Drug and Biological Product Inspections During COVID-19 Public Health Emergency Questions and Answers (August 2020)
- Review Timelines for Applicant Responses to Complete Response Letters When a Facility Assessment Is Needed During the COVID-19 Public Health Emergency Guidance for Industry (December 2020)

EU/EMA

During the national or international crises of the COVID-19 pandemic, on-site GMP/GDP inspections may not be possible for a number of reasons such as travel restrictions, risk to health, or other restrictions/guidance issued by local or national authorities. In this context, for sites in the European Economic Area (EEA), GMP certificates and time-limited manufacturing and import authorizations are automatically extended until the end of 2021. This does not waive manufacturers' and importers' obligations to comply with GMP standards.

For new sites and facilities within and outside the EEA that have not been inspected or where an inspection is required, distant assessment is recommended to represent a suitable means of determining compliance with the principles and guidelines of GMP, which can be considered for all types of inspections as necessary and can be performed for all types of sites and dosage forms following a careful case-by-case evaluation, taking into account the criticality of the manufacturing activities and the product(s) concerned.

On-site inspections should be conducted when circumstances permit following the distant assessment; the scheduling should be based on risk management principles, and priority should be given to sites which have never been inspected on-site before by an EEA inspectorate or by an MRA partner authority, and to sterile manufacturing processes.

Key updates are listed as follows:

- Questions and Answers on Regulatory Expectations for Medicinal Products for Human Use during the COVID-19 Pandemic (Updated: July 2020)
- Guidance Related to GMP/GDP and PMF Distant Assessments (November 2020)

WHO

This draft guideline *Good Manufacturing Practices for Investigational Products* posted in November 2020 revised the *WHO Good Manufacturing Practices for Investigational Pharmaceutical Products for Clinical Trials in Humans* due to the urgent need, raised by WHO's Prequalification Team – Inspections Services, for new guidelines arising from inspections carried out for COVID-19 therapeutics. The objective of this update is to bring the guideline in line with current expectations and trends in good manufacturing practices and to harmonize the text with the principles from other related international guidelines.

The draft guideline requests manufacturers to establish a system for quality risk management, ultimately to the protection of the trial subject and patient. The draft guideline also states that qualification and validation required for investigational products should be guided by risk assessment.

Written procedures for recall and complaint handling should also be established for investigational products.