Relevant WHO technical guidance documents for COVID-19 vaccines and other biologicals

(Version 10 December 2021)

This table provides examples of existing WHO guidance documents adopted by WHO Expert Committee on Biological Standardization, published in Technical Report Series (TRS) [1], that may provide useful guidance and information for the development, production and evaluation of candidate COVID-19 vaccines[2]. This list is not exhaustive but focused on evaluation of vaccines. Some guidelines may also be applicable for other COVID-19 interventions such as therapeutic products (e.g. antibodies).

[1]Available on: https://www.who.int/teams/health-product-policy-and-standards/standards-and-specifications/trs-publications-listing

[2]Refer to WHO Blueprint information: https://www.who.int/blueprint/priority-diseases/key-action/novel-coronavirus/en/. As shown, multiple COVID-19 vaccine candidates use same/similar platforms as for the other vaccines for which there are established WHO guidance.

WHO Guidelines/Recommendations	Scope of document and highlights identified that may be relevant to COVID-19 vaccines	Applicability/product type(s)
Guidelines/Recommendations for other vaccines that may share the same/similar platforms as for COVID-19 vaccine candidates		
Evaluation of the quality, safety and efficacy of messenger RNA vaccines for the prevention of infectious diseases: regulatory considerations. 2021	The scope of this document is limited to **mRNA** and self-amplifying mRNA, packaged in lipid nanoparticles **(LNP)**, for in vivo delivery of the coding sequences of a target antigen relevant to active immunization for the prevention of an infectious disease. This document provides information and regulatory considerations regarding key aspects of the **manufacture and quality control, and nonclinical and clinical evaluation, of preventive mRNA vaccines against infectious disease for human use**.	Messenger RNA vaccines

Guidelines for assuring the quality, safety, and efficacy of plasmid DNA vaccines. TRS No. 1028, Annex 2 2020	- This document provides guidance on **quality, nonclinical, and clinical aspects of DNA vaccines** (including plasmids encoding adjuvant molecules, if present) intended for use in humans to prevent infectious diseases. - The revised guidelines are unlikely to be applicable to vaccines based on RNA because different requirements are likely to apply for quality, nonclinical, and clinical testing for these types of vaccines and immunotherapeutics. WHO is in the process to develop regulatory considerations for RNA vaccines.	DNA vaccines
Guidelines on the quality, safety and efficacy of respiratory syncytial virus vaccines, WHO TRS No. 1024, Annex 2. 2019	- Provide guidance to NRAs and vaccine manufacturers on the manufacturing processes and nonclinical and clinical evaluation of human RSV vaccines required to assure their quality, safety and efficacy. - The scope encompasses **broad range of technologies /platforms** of vaccine development and production (see right column), particularly for each of them, key quality control considerations are provided in CMC aspects (see Part A of the Guidelines). - In particular, include extensive discussions and regulatory considerations about **vaccine-associated enhanced respiratory diseases** in the context of RSV vaccines (nonclinical evaluation and clinical evaluation aspects)	- live attenuated vaccines/chimeric virus vaccines - vaccines produced using recombinant viral and other vectored systems - protein-based vaccines (including subunit and nanoparticle formulations with and without adjuvants)

Guidelines on the quality, safety and efficacy of Ebola vaccines, Annex 2, TRS No. 1011, 2017	- Provide scientific and regulatory guidance for national regulatory authorities (NRAs) and vaccine manufacturers on the quality, nonclinical and clinical aspects of Ebola vaccines relevant to marketing authorizations. - Focus on Ebola vaccines based on viral vectors. Some principles may be applicable for other platforms. • viral vectors used to develop Ebola vaccines including replicating and non-replicating are covered by the Guidelines. - Discuss opportunities to accelerate vaccine development and product availability during a public health emergency, consider the principles which may be applied to product development, manufacturing and control – and to nonclinical and clinical evaluation – During **a public health emergency** to allow for the rapid introduction of an Ebola vaccine. Wherever appropriate, discussions on the minimum dataset required are highlighted and aspects of vaccine development which may be accelerated during a public health emergency are indicated. - Provide a Section on: **Accelerated availability of vaccines during a public health emergency – general principles** - In particular, regarding **animal challenge studies**, provide sections on "Use of a challenge-protection animal study to support licensure", and "Animal efficacy data for demonstration of effectiveness".	Recombinant viral vectored vaccines
Guidelines on the quality, safety and efficacy of biotherapeutic protein products prepared by	-These WHO Guidelines provide guidance to NRAs and manufacturers on the quality, nonclinical and clinical aspects of **rDNA-derived** biotherapeutic protein products for the purpose of licensing.	Biologically active protein products prepared by rDNA technology and used for the purposes indicated in left column.

recombinant DNA technology, WHO TRS No. 987, Annex 4. 2013	-The Guidelines apply, in principle, to all biologically active protein products which are used in the treatment of human diseases and which are prepared by **rDNA technology** using prokaryotic or eukaryotic cells. -The Guidelines also apply to protein products used for **in vivo diagnosis** (e.g. monoclonal antibody products used for imaging), products used for ex-vivo treatment, and those intentionally modified by, for example, PEGylation, conjugation with a cytotoxic drug, or modification of rDNA sequences. Some aspects of these Guidelines may apply to products produced in transgenic animals and plants products for the purpose of licensing. Some aspects of manufacturing and quality control in these Guidelines may apply to **protein-based vaccine antigens made by rDNA technology**.	Biotherapeutic products including monoclonal antibodies, erythropoietin, growth hormones, interferons. **Protein-based vaccine antigens made by rDNA technology**.
WHO generic Guidelines/Recommendations that are applicable for all biological products including vaccines: development, production, regulation		
Recommendations for the Evaluation of Animal Cell Cultures as Substrates for the Manufacture of Biological Medicinal Products and for the Characterization of Cell banks. WHO TRS No. 978, Annex 3. 2010	Provide guidance to NRAs, national control laboratories (NCLs) and manufacturers on the evaluation of animal cell cultures used as substrates for the production of biological medicinal products, and for the characterization of cell banks.	All biological products including vaccines produced via animal cell substrates. A number of generic issues apply to genetically modified and other cell substrates.

WHO good manufacturing practices for biological products, WHO TRS No. 999, Annex 2. 2015	The guidance applies to the manufacture, control and testing of biological products for human use – from starting materials and preparations (including seed lots, cell banks and intermediates) to the finished product. Manufacturing procedures within the scope of this document include: - growth of strains of microorganisms and eukaryotic cells; - extraction of substances from biological tissues, including human, animal and plant tissues, and fungi; - recombinant DNA techniques; - hybridoma techniques; - propagation of microorganisms in embryos or animals.	Biological products including vaccines for human use
Guidelines on procedures and data requirements for changes to approved vaccines, TRS No. 993, Annex 4, 2015	Provides guidance for NRAs and MA holders on the regulation of changes to the original MA dossier or product licence for an approved vaccine in terms of: (a) procedures and criteria for the appropriate categorization and reporting of changes; and (b) the data required to enable NRAs to evaluate the impact of the change on the quality, safety and efficacy of the vaccine. Additionally, the purpose of these WHO Guidelines is to assist NRAs in establishing regulatory procedures for post-approval changes to vaccines. The guidance given below applies to the manufacture and use of approved prophylactic vaccines for humans. However, the general principles set out in this document may also apply to other biological products.	Vaccines

Guidelines on procedures and data requirements for changes to approved biotherapeutic products, TRS No 1011, Annex 3, 2018	These WHO Guidelines provide guidance for NRAs and marketing authorization holders on the regulation of changes to the original marketing authorization dossier or product licence for an approved biotherapeutic product in terms of: (a) the procedures and criteria for the appropriate categorization and reporting of changes; and (b) the data required to enable NRAs to evaluate the potential impact of the change on the quality, safety and efficacy of the product.	Biotherapeutic products
Guidelines for independent lot release of vaccines by regulatory authorities, WHO TRS No. 978, Annex 2. 2010	- The document is intended to provide guidance to the NRAs/NCLs and to vaccine manufacturers. It may also be relevant to public health authorities such as a national immunization programme. - PHE was considered: "All vaccine lots should be released by an NRA/NCL; however, in defined exceptional circumstances such as a **public health emergency, exemption could be allowed**. The permitted circumstances and the procedures to be followed to ensure quality in the absence of lot release should be covered by legal provisions."	Vaccines
Guidelines on stability evaluation of vaccines, WHO TRS No. 962, Annex 3. 2006	Provide the scientific basis and guiding principles for evaluation of vaccine stability for the purpose of clinical trial approval, licensing, post-licensure stability monitoring and thermal stability testing for lot release.	Vaccines

WHO Guidelines on Transmissible Spongiform Encephalopathies in relation to Biological and Pharmaceutical Products. 2003	WHO guidelines to minimize the risks associated with the use of vaccines, blood products and other pharmaceutical products containing bovine-derived and human-derived materials, were updated in 2003 following a review of the latest available data on the epidemiology, ante-mortem and post-mortem diagnosis, detection of the infectious agents, and distribution of infectivity in tissues or body fluids of relevant species with TSEs. Provide guidance on control of animal and human components used in culture medium during production.	Biological and pharmaceutical products
WHO generic Guidelines/Recommendations that are applicable for all vaccines: Non-clinical evaluation		
WHO guidelines on nonclinical evaluation of vaccines, WHO TRS No. 927, Annex 1. 2005	-General principles of nonclinical evaluation of vaccines are discussed, with particular attention being given to the regulatory expectations for **new and novel vaccines**. -Nonclinical evaluation, within the context of this document, refers to **all in vivo and in vitro testing performed before and during the clinical development of vaccines**. Scope: both prophylactic and therapeutic vaccines for infectious disease indications are considered in this document. Vaccines for human use include one or more of the following: • microorganisms inactivated by chemical and/or physical means that retain appropriate immunogenic properties; • living microorganisms that have been selected for their attenuation whilst retaining immunogenic properties; • antigens extracted from microorganisms, secreted by them or produced by recombinant DNA technology;	Prophylactic and therapeutic vaccines for infectious disease indications, particular **new and novel vaccines**

	• chimeric microorganisms; • antigens produced in vivo in the vaccinated host following administration of a live vector or nucleic acid or antigens produced by chemical synthesis in vitro. The antigens may be in their native state, truncated or modified following introduction of mutations, detoxified by chemical or physical means and/or aggregated, polymerized or conjugated to a carrier to increase immunogenicity. Antigens may be presented plain or in conjunction with an adjuvant, or in combination with other antigens, additives and other excipients.	
Guidelines on the nonclinical evaluation of vaccine adjuvants and adjuvanted vaccines, WHO TRS No. 987, Annex 2. 2013	- The goal of this document is to provide consistent and harmonized guidance on nonclinical testing approaches to support the use of candidate adjuvanted vaccines in all stages of clinical development and ultimately for marketing authorization of the product. - Excerpt: "Adjuvants are also used in antigen dose-sparing strategies with the aim of increasing the availability and supply of vaccines – **for example, under emergency situations of an influenza pandemic** or as a strategy to decrease the cost of the vaccine (e.g. use of inactivated poliovirus vaccine for polio eradication)."	Both prophylactic and therapeutic vaccines with adjuvants
WHO Guidelines/Recommendations that are applicable for all vaccines: Clinical evaluation		

Guidelines on clinical evaluation of vaccines: regulatory expectations, WHO TRS No. 1004, Annex 9. 2016	These WHO Guidelines consider clinical development programmes for vaccines that are intended to prevent clinical disease in humans by eliciting protective immune responses. The protective immune response to vaccination may be directed against one or more specific antigenic components of microorganisms or against substances produced and secreted by them that are responsible for clinical disease. These Guidelines are applicable to the clinical development of: • new candidate vaccines; • licensed vaccines; • vaccines that are given by any route of administration; • vaccines that may be given before exposure or shortly after known or presumed exposure to an infectious agent to prevent the onset of clinical disease.	Vaccines (prophylactic)
Human challenge trials for vaccine development: regulatory considerations, WHO TRS No. 1004, Annex 10. 2016	- Provide guidance to NRAs, manufacturers, vaccine developers, investigators and independent ethics committees – and potentially to biosafety committees and national agencies that regulate genetically modified organisms (GMOs) where separate from the NRA. - The document covers issues specifically relevant to the design and conduct of clinical trials that enroll healthy adult humans capable of truly informed consent, and that involve the intentional exposure to, and potential infection with, an infectious disease organism.	Vaccines

	- One of the potential purposes of HCT is **"support for emergency use of an investigational vaccine (for example, during an influenza pandemic)"**	
WHO Guidelines/Recommendations on regulatory preparedness in response to a pandemic/PHE		
Regulatory preparedness for human pandemic influenza vaccines, WHO TRS No. 963, Annex 2. 2007	The guidelines are intended to provide both national regulatory authorities and vaccine manufacturers with the most up-to-date advice concerning regulatory pathways for **pandemic influenza vaccines**; regulatory considerations to take into account in evaluating the quality, safety and efficacy of vaccine candidates; and requirements for effective postmarketing surveillance of pandemic influenza vaccines.	**Regulatory preparedness in a pandemic** in context of influenza vaccines
Guidelines on regulatory preparedness for provision of marketing authorization of human pandemic influenza vaccines in non-vaccine-producing countries, WHO TRS No. 1004, Annex 7. 2016	-Provide guidance to NRAs of **non-vaccine-producing countries** on the regulatory oversight of **pandemic influenza vaccines for use in public health emergencies.** - Focus in particular on the needs of countries that are not producing influenza vaccines, including countries supplied with vaccines through United Nations agencies and countries which self-procure vaccines	**Regulatory preparedness in a pandemic** in context of influenza vaccines
Other examples of WHO Guidelines/Recommendations for various types of vaccines- Available on: https://www.who.int/teams/health-product-and-policy-standards/standards-and-specifications/vaccine-standardization/		

Enterovirus 71 (TRS 1030, A3) Rabies (TRS 941, A2) Tick-bone encephalitis (TRS 889, A2) HAV (TRS 858, A2) JE (TRS 963, A1) Influenza (TRS 927, A3)	**Inactivated vaccines**
Influenza (subunit, TRS 927, A3) HBV (TRS 978, A4) Malaria (TRS 980, A3) HPV (TRS 999, A4) HEV (TRS 1016, A2)	**Protein-based vaccines (e.g. protein, subunit, VLP)**
Rotavirus (TRS 941, A3) Influenza (TRS 977, A4) Yellow fever (TRS 978, A5) Dengue (TRS 979, A2) JE (TRS 980, A7)	**Live attenuated vaccines**