世界卫生组织2019冠状病毒病（COVID-19）疫苗的目标产品特性

2020年4月9日

目的

特定的疾病领域会被确立为世界卫生组织（World Health Organization，WHO）的研究与产品开发重点。针对2019冠状病毒病（ Corona Virus Disease 2019，COVID-19），其相关疫苗产品的目标产品特性的制定工作已于*“COVID-19全球研究与创新论坛：制定研究路线图”*会议举办之后启动。本文件面向的读者包括：疫苗科学家、疫苗产品研发机构、疫苗生产机构和出资机构等。

WHO的政策建议和预认证（ Prequalification，PQ）指南中的各项要求也将一并适用。下文所列内容为WHO今后对COVID-19疫苗逐个开展评估时将考虑的一些相关标准。

因此，若某种疫苗的特性足够优于单个或多个类别项下的关键特性要求，虽其未能满足其他某项特定的关键特性要求，但仍有可能因前者而获得积极的考虑。多项关键特性要求均无法满足的候选疫苗则不太有望在WHO的评估程序中获得有利的结果。

关于WHO PQ程序的一般性说明详见文末。

为进一步改进疫苗产品的理想特性，应当采取的优先工作是：在疫情的不同阶段，对具有不同有效性以及采用不同的免疫策略进行接种的COVID-19疫苗，做潜在影响力的模型分析。针对某些疫苗特性，本文通过脚注的方式补充介绍了相关的原理与所做出的假设。

致谢

在公开征求意见阶段，有多位专家与机构对本文件的草案提出了宝贵的意见。WHO在此表示感谢。

一、背景介绍

2019年12月31日，WHO收到中国湖北省武汉市发现了一起不明原因聚集性肺炎病例事件的通报。2020年1月7日，中国确认了COVID-2019的病原体。截至2020年4月10日，全球范围内已累计出现160多万例病例，相关死亡人数约10万人。

2020年2月11日至12日，相关学科的全球知名专家在WHO日内瓦总部召开会议，以评估目前对新型病毒的认识水平，并就亟待解决的重大研究问题，以及如何共同加快和资助有助于遏制当前疫情暴发，并为未来防疫工作做好准备等优先研究事项达成共识。

本文描述了针对COVID-2019的人用疫苗产品在两种使用情况下的理想及最低可接受的特性要求：用于面临持续高风险暴露的人群（如医护工作者）的长期保护，以及在疫情暴发情况下为达到快速免疫效果的应急使用。

本目标产品特性（Target Product Profile，TPP）的制定经过了与人类和动物健康、科研、资助和生产部门等主要利益攸关方的协商。其目的是为了指导并优先推进相关疫苗产品的开发。随着新的科学证据产生，本TPP可能还需进一步修订。

二、TPP

*路线图战略目标：开发并许可*在疫情暴发期间开展应急接种和/或针对持续面临COVID-2019高风险暴露人员具有长期保护效果的疫苗。

疫苗特性	理想特性	关键特性或最低要求
适应证	疫情暴发：用于为正在暴发疫情地区的高危人群进行主动免疫，以预防新型冠状病毒（SARS-CoV-2）感染；与其他防控措施一同使用，以遏制或终止疫情暴发。 长期保护：用于高危人群的主动免疫，以预防COVID-2019。	疫情暴发：用于为正在暴发疫情地区的高危人群进行主动免疫，以预防COVID-2019；与其他防控措施一同使用，以遏制或终止疫情暴发。 长期保护：用于高危人群的主动免疫，以预防COVID-2019。
禁忌	无。	可接受存在一些禁忌证（如免疫功能低下）。
目标人群	所有年龄段[1]。 适用于孕妇及哺乳期女性。	成人，包括老年人。
安全性/ 反应原性	具有足够的安全性和反应原性，基于观察到的疫苗保护效力，具有很高的收益风险比。 只有疫苗接种相关的轻微、短暂的不良事件，无严重不良事件。	疫情暴发：安全性和反应原性可让疫苗的收益高于安全风险[2]。 长期保护：具有足够的安全性和反应原性，基于观察到的疫苗保护效力，具有很高的收益风险比。只有疫苗接种相关的轻微、短暂的不良事件。

[1] 认为群体免疫（和传播的阻断）将取决于大范围的预防接种，很可能包括儿童。

[2] 收益/风险可能取决于年龄等其他因素。收益/风险的评估应考虑到疾病增强作用的可能性。

保护效力的衡量	不低于70%的保护效力（以群体为基础，在老年人群中的效果具有一致性）[3]。 观察终点可以是比较评估患病、重症和/或排毒/传播能力。 疫情暴发：快速起效，以提供保护（两周之内）。 长期保护：快速起效不是重要因素。	明确显示有保护效力（以群体为基础），理想的是具有约50%的点估计值[3]。 观察终点可以是比较评估对患病、重症和/或排毒/传播能力[4]。
剂量方案	疫情暴发：1剂基础免疫[5]。 长期保护：优先选择加强免疫频率更少（1年1次或频率更低）的疫苗。	疫情暴发：不超过2剂的方案[6]。 长期保护：允许加强免疫剂次。
保护持久性	提供至少1年的保护。	提供至少6个月的保护[7]。
接种途径	疫情暴发：为易于实现快速接种，并出于其他后勤考虑，优先选择非注射方式（避免使用注射器/针头或其他辅助设备）。 长期保护：任何接种途径均可接受。	只要疫苗安全有效，任何接种途径都可接受。
产品的稳定性和储存	易于管理 较高储存温度和具有较强热稳定性的疫苗可显著提升疫苗可分发性与可及性，因此最为理想。	疫情暴发：在-60℃-70℃[8]以下温度有效期至少12个月，并证明可在2-8℃之间的温度下保持至少2周的稳定性。 长期保护：在-20℃或更高的温度

[3] 有效性估计的置信度下限有可能更低。

[4] 如果监管部门在临床保护效力数据尚不完备的情况下提供授权，则须在疫苗使用过程中收集保护效果数据。

[5] 请注意：虽强烈偏向于采用单剂疫苗，但如果两剂次程序疫苗才具有可行性，则也不希望抑制两剂次程序疫苗的开发。

[6] 请注意：霍乱是两剂次程序疫苗，而很多两剂次程序疫苗在接种单剂后即可获得部分保护。对于两剂次程序疫苗而言，应评估接种一剂后的保护效果。

[7] 最初的临床研究可能无法证实这一效果，但可以通过后续的研究和动物试验数据等提供依据。

[8] 对于药物产品，在低于零下20摄氏度的温度下储存需要更多的基础设施保障，可能妨碍疫苗的流通分发，因此需要注意这一问题。

	疫苗温度指示标签（Vaccine Vial Monitor，VVM）：证明在容器上使用VVM的可行性与意向。	下储存； VVM：说明在容器上使用VVM的可行性与意向。
与其他疫苗的联合接种	疫情暴发：独立的产品。 长期保护：有与其他疫苗（如：流感、脊髓灰质炎、麻疹、肺炎球菌等）联合接种的可能。	独立的产品。
规格	疫情暴发：为便于在群体性接种中使用，优先选择多人份包装。 长期保护：可接受多人份或单人份包装。 注射用最大剂量：0.5 毫升。 多人份包装规定配制、管理和废弃应遵循WHO的多人份包装的政策[9]。	疫情暴发：可接受多人份或单人份包装。 注射用最大剂量：1 毫升。 多人份包装规定配制、管理和废弃应遵循WHO的多人份包装的政策。
注册和预认证	疫情暴发：通过WHO预认证并/或符合《紧急使用评估和清单程序》（EUAL）项下的标准。 长期保护：通过WHO预认证。	疫情暴发：满足WHO预认证及/或《紧急使用评估和清单程序》（EUAL）的标准 。 长期保护：通过WHO预认证。
可及性	疫情暴发：在允许广泛使用的成本下，包括中低收入国家（LMIC）使用，有能力快速扩大生产规模。 长期保护：在允许广泛使用的成本下，包括中低收入国家（LMIC）使用，能够提供充足的疫苗。	疫情暴发：在允许广泛使用的成本下，包括中低收入国家（LMIC）使用，有能力快速扩大生产规模。 长期保护：在允许广泛使用的成本下，包括中低收入国家（LMIC）使用，能够提供充足的疫苗。

[9] 如具可行性，则满足“开瓶”规定（open vial policy）的疫苗可能更具有优势。

三、关于人用疫苗方案适宜性的考虑

WHO预认证

由联合国各大机构采购或全球疫苗免疫联盟（GAVI）等其他机构资助的疫苗需要通过WHO预认证（WHO-PQ）。WHO预认证的作用是对纳入中低收入国家免疫规划的疫苗质量、安全性、有效性和适宜性做出国际性的保证。WHO鼓励疫苗研发和生产机构尽早（即使是在研发的早期阶段）了解其预认证程序的详情，并在进入预认证申请程序的早期，与WHO负责预认证的工作人员探讨拟申请的产品与监管要求。WHO在考虑任何预认证资格时，需要其已经获得国家监管机构（NRA）或欧洲药品管理局（如果为在欧洲集中上市的授权程序）所颁发的许可。

此外，预认证程序需要获得NRA的备案审批。NRA通常是指疫苗生产国或疫苗制造与销售所在国的国家监管机构，并且上述国家监管机构应已通过WHO的正常运行评估。疫苗研发机构应确认，预认证程序中拟涉及的国家监管机构已获得WHO的认可。

预认证程序在联合国机构采购疫苗的可接受性评估程序（WHO技术报告系列（TRS）第 978 号文）中有详细的说明。可点击以下链接查阅：
http://apps.who.int/medicinedocs/documents/s21095en/s21095en.pdf。

WHO预认证程序的目的是评估用于中低收入国家的疫苗产品的质量、安全性、有效性和适宜性。程序设置了被称为“预认证的方案适宜性”（PSPQ）标准，用于审查申请预认证的疫苗产品。（http://apps.who.int/iris/bitstream/10665/76537/1/WHO_IVB_12.10_eng.pdf）

预认证实施适宜性的考虑

除满足质量、安全性和有效性的要求之外，研发和生产机构还必须了解WHO一贯青睐的可直接提升预防接种实施效果的各项指标。若新疫苗的实施适宜性偏低，则可导致延迟纳入常规免疫项目。例如，推出包装过大或容量偏高、稳定性偏低的新疫苗会对冷链的能力或处置需求产生极大的影响，因此可能会对现有预防接种的正常运行产生不利的影响。因此，建议申请人在早期阶段便考虑好规格和包装的参数。

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原文地址：https://www.who.int/blueprint/priority-diseases/key-action/WHO_Target_Product_Profiles_for_COVID-19_web.pdf?ua=1

WHO Target Product Profiles for COVID-19 Vaccines

9 April 2020

Purpose of the document

Selected disease areas are identified as WHO priorities for research and product development. In the case of COVID-19, target product profile development followed the COVID-19 Global research and innovation forum: towards a research roadmap. The target audience includes vaccine scientists, product developers, manufacturers and funding agencies.

All the requirements contained in WHO guidelines for WHO policy recommendation and prequalification will also apply. The criteria below lay out some of the considerations that will be relevant in WHO's case-by-case assessments of COVID-19 vaccines in the future.

Therefore, should a vaccine's profile be sufficiently superior to the critical characteristics under one or more categories, this may outweigh failure to meet another specific critical characteristic. Vaccines which fail to meet multiple critical characteristics are unlikely to achieve favourable outcomes from WHO's processes.

A generic description of WHO's Vaccine Prequalification process can be found at the end of this document.

Modelling of the potential impact of COVID-19 vaccines with different efficacy profiles, administered using different immunization strategies, at different stages of the epidemic is a high priority to further refine desired characteristics. For certain vaccine characteristics, additional footnotes are provided on the rationale and assumptions made.

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I. Background

On 31 December 2019, WHO was informed of a cluster of cases of pneumonia of unknown cause detected in Wuhan City, Hubei Province of China. The coronavirus disease (COVID-2019) was identified as the causative virus by Chinese authorities on 7 January. As of 10 April 2020, there have been over 1.6 million cases and almost 100,000 deaths world-wide.

World-renowned experts in relevant disciplines met at the World Health Organization's Geneva headquarters from 11 to 12 February 2020 to assess the current level of knowledge about the new virus, agree on critical research questions that need to be answered urgently and ways to work together to accelerate and fund priority research that can contribute to curtail this outbreak and prepare for future outbreaks.

This document describes the preferred and minimally acceptable profiles for human vaccines for long term protection of persons at high ongoing risk of COVID-19 such as healthcare workers and for reactive use in outbreak settings with rapid onset of immunity.

This Target Product Profile (TPP) was developed through a consultation process with key stakeholders in human and animal health, scientific, funding and manufacturing communities. It is intended that it will guide and prioritize the development of vaccines. As new scientific evidence is generated, this TPP may require further review and revision.

II. Target Product Profiles

Roadmap strategic goal: Develop and license vaccines **for reactive use in outbreak settings (Outbreak) and/or** with **long-term protection for administration to those at high ongoing risk of COVID-19 (LT).**

Vaccine characteristic	**Preferred**	**Critical or Minimal**
Indication for use	Outbreak: For active immunization of at-risk persons in the area of an on-going outbreak for the prevention of infection of SARS-CoV-2; to be used in conjunction with other control measures to curtail or end an outbreak. LT: For active immunization of at-risk persons to prevent COVID-19	Outbreak: For active immunization of at-risk persons in the area of an on-going outbreak for the prevention of COVID-19; to be used in conjunction with other control measures to curtail or end an outbreak LT: For active immunization of at-risk persons to prevent COVID-19
Contraindication	None	Some contraindications (e.g., immunocompromised) may be acceptable
Target population	All ages[1]. Suitable for administration to pregnant and lactating women.	Adults, including elderly
Safety/Reactogenicity	Safety and reactogenicity sufficient to provide a highly favourable benefit/risk profile in the context of observed vaccine efficacy; with only mild, transient adverse events related to vaccination and no serious AEs.	Outbreak: Safety and reactogenicity whereby vaccine benefits outweigh safety risks[2]. LT: Safety and reactogenicity sufficient to provide a highly favourable benefit/risk profile in the context of observed vaccine efficacy; with only mild, transient adverse events related to vaccination.

[1] Recognize that herd immunity (and transmission blocking) will depend on broad immunization, likely including children.

[2] Benefit/risk may depend on age, other factors. Benefit/risk assessment should take potential for enhanced disease into account

Measures of Efficacy	At least 70% efficacy (on population basis, with consistent results in the elderly)[3]. Endpoint may be assessed vs. disease, severe disease, and/or shedding/transmission. Outbreak: Rapid onset of protection (less than 2 weeks). LT: rapid onset of protection is less important	Clear demonstration of efficacy (on population basis) ideally with ~50% point estimate[3]. Endpoint may be assessed vs. disease, severe disease, and/or shedding/transmission[4].
Dose regimen	Outbreak:Single-dose primary series[5]. LT: Lower frequency (Yearly or less) of booster doses is preferred	Outbreak: No more than two dose regimen[6] LT: Booster doses permitted
Durability of protection	Confers protection for at least 1 year.	Confers protection for at least 6 months[7].
Route of Administration	Outbreak: Non-parenteral (syringe/needle or other adjunct equipment-avoiding) is preferred for ease of rapid administration and other logistical issues. LT: any route of administration is acceptable	Any route of administration is acceptable, if vaccine is safe and effective.
Product Stability and Storage	Higher storage temperatures and higher thermostability will greatly enhance vaccine	Outbreak: Shelf life of at least 12 months as low as -60—70°C[8], and

[3] The lower confidence limit of the efficacy estimate could be lower

[4] If regulatory authorization is provided with incomplete clinical efficacy data, effectiveness data are to be generated during use

[5] Note strong preference for single-dose, but do not desire to discourage development of 2-dose vaccines if that is what is feasible

[6] note cholera is 2 dose, and many 2 dose vaccines confer partial protection after a single dose. For two-dose vaccines, protection after single dose should be assessed

[7] This might not be demonstrated in initial clinical studies, but could be supported by follow-on studies, animal data, etc

[8] For drug product, storage at temperatures below -20C would require additional infrastructure and may impede distribution of vaccine, and would thus need to be addressed.

	distribution and availability, and are thus strongly preferred. Vaccine vial monitor (VVM): Proof of feasibility and intent to apply a VVM to the primary container.	demonstration of at least 2-week stability at 2-8°C. LT: Storage at -20°C or higher; Vaccine vial monitor (VVM): Proof of feasibility and intent to apply a VVM to the primary container.
Co-administration with other vaccines	Outbreak: stand alone product LT: potential for coadministration with other vaccines (e.g, flu, polio, measles, pneumococcal) preferred	Stand-alone product
Presentation	Outbreak: Multi-dose presentation is preferred for ease of use in campaigns. LT: mono-dose or multi-dose presentations are acceptable	:Multi- or mono- dose presentations are acceptable.
	Maximum parenteral dose volume: 0.5 mL Multi-dose presentations should be formulated, managed and discarded in compliance with WHO's multi-dose vial policy[9].	Maximum parenteral dose volume: 1 mL Multi-dose presentations should be formulated, managed and discarded in compliance with WHO's multi-dose vial policy.
Registration and Prequalification	Outbreak: WHO pre-qualified and/or meets criteria for EUAL LT: WHO pre-qualified	Outbreak: Meets criteria for WHO prequalification and/or EUAL LT: WHO pre-qualified
Accessibility	Outbreak: Capability to rapidly scale-up production at cost/dose that allows broad use, including in LMIC.	Outbreak: Capability to rapidly scale-up production at cost/dose that allows broad use, including in LMIC.

[9] If feasible, vaccines consistent with an "open vial" policy may have additional advantages

LT: Availability of sufficient doses at cost/dose that allows broad use, including in LMIC	LT: Availability of sufficient doses at cost/dose that allows broad use, including in LMIC

III. Considerations on Programmatic suitability

Vaccine for human use

WHO Prequalification

Vaccines that are procured by United Nations agencies and for financing by other agencies, including Gavi, the vaccine alliance, require WHO Prequalification. The WHO prequalification (PQ) process acts as an international assurance of quality, safety, efficacy and suitability for low and middle-income country immunization programs. WHO encourages vaccine developers and manufacturers to be aware of the WHO prequalification process, even at the early stages of development and to discuss the product and the regulatory requirements with the WHO prequalification staff early in the process. Licensure by a national regulatory authority (NRA), or European Medicines Agency in the case of the centralized procedure for marketing authorization in Europe, will be required prior to any consideration of prequalification. Furthermore, the prequalification process requires regulatory oversight by the NRA of Record, which is usually the NRA of the country where the vaccine is manufactured or the NRA of the country of finishing and distribution, and such an NRA should have been assessed as functional by WHO. Vaccine developers should check that the planned NRA of Record for the prequalification procedure is considered functional by WHO.

The prequalification procedure is described in detail in the document Procedures for assessing the acceptability, in principle, of vaccines for purchase by United Nations agencies (WHO TRS 978) available here: http://apps.who.int/medicinedocs/documents/s21095en/s21095en.pdf. The WHO PQ process which assesses vaccine quality, safety, efficacy and suitability for use in low and middle-income countries has developed criteria called Programmatic Suitability for Prequalification (PSPQ) criteria to review vaccines submitted for prequalification. (http://apps.who.int/iris/bitstream/10665/76537/1/WHO_IVB_12.10_eng.pdf).

Considerations of Programmatic Suitability for Prequalification

In addition to meeting quality, safety and efficacy requirements, it is also important that developers and manufacturers understand WHO's preferences for parameters that have a direct operational impact on immunization programs. Low programmatic suitability of new vaccines could result in delaying introduction in routine immunization programmes. for example, introduction of new vaccines that have higher packaging or presentation volumes, low formulation stability will highly impact on cold chain capacity or disposal demands therefore may have negative impact on existing operations of immunization programs. Therefore, early stage consideration of presentation and packaging parameters is encouraged.