

## INDICATIVE LIST OF TRADE-RELATED BOTTLENECKS AND TRADE-FACILITATING MEASURES ON CRITICAL PRODUCTS TO COMBAT COVID-19<sup>1</sup>

### INFORMATION NOTE<sup>2</sup>

#### 1. INTRODUCTION

This information note seeks to facilitate access to information on possible trade-related bottlenecks and trade-facilitating measures on critical products to combat COVID-19, including inputs used in vaccine manufacturing, vaccine distribution and approval, therapeutics and pharmaceuticals, diagnostics and medical devices. It is not meant to be an exhaustive list of all specific trade measures, nor does it make any judgement on the effect or significance of the reported bottlenecks, nor on the desirability of implementing any of the suggestions on trade-facilitating measures.<sup>3</sup>

The indicative list is based on issues identified and suggestions made by stakeholders at various events and consultations convened by the WTO, as well as with vaccine manufacturers in the context of meetings organized by the Multilateral Leaders Task Force on COVID-19,<sup>4</sup> which includes the heads of the International Monetary Fund (IMF), the World Bank Group, the World Health Organization (WHO) and the WTO.<sup>5</sup> This revision includes information as of 4 October 2021. Entries under each subheading are presented in no particular order. One common theme that emerges is that essential goods and inputs need to flow efficiently and expeditiously to support the rapid scaling up of COVID-19 production capacity worldwide. As manufacturers scale up production and establish new sites in different countries, the production network is not only becoming larger but also increasingly complex and international. The delay of a single component may significantly slow down or even bring vaccine manufacturing to a halt, so it follows that inputs need to flow expeditiously, and each node within the supply chain network needs to operate seamlessly with the others.

The information note is intended to be a living list. Comments, clarifications, modifications and improvements are actively sought. To contribute with inputs that may be incorporated in future updates, please contact Mr Roy Santana ([Roy.Santana@wto.org](mailto:Roy.Santana@wto.org)) or Mr Devin McDaniels ([Devin.McDaniels@wto.org](mailto:Devin.McDaniels@wto.org)).

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<sup>1</sup> This is a revision of the original note, dated 20 July 2020. It reflects information available until 4 October 2021.

<sup>2</sup> This document has been prepared under the WTO Secretariat's own responsibility and is without prejudice to the positions of WTO members or to their rights and obligations under the WTO.

<sup>3</sup> In the context of the Trade Monitoring Exercise, the WTO Secretariat maintains a list of trade and trade-related measures taken in the context of the COVID-19 pandemic: see [https://www.wto.org/english/tratop\\_e/covid19\\_e/trade\\_related\\_goods\\_measure\\_e.htm](https://www.wto.org/english/tratop_e/covid19_e/trade_related_goods_measure_e.htm).

<sup>4</sup> See <https://www.covid19taskforce.com/en/programs/task-force-on-covid-19-vaccines>.

<sup>5</sup> These include: WTO webinar Regulatory Cooperation during the COVID-19 Pandemic, on 2 June 2021, ([https://www.wto.org/english/news\\_e/news21\\_e/trip\\_28may21\\_e.htm](https://www.wto.org/english/news_e/news21_e/trip_28may21_e.htm)); the WTO symposium COVID-19 Vaccine Supply Chain and Regulatory Transparency, on 29 June 2021 ([https://www.wto.org/english/tratop\\_e/trips\\_e/technical\\_symposium\\_2906\\_e.htm](https://www.wto.org/english/tratop_e/trips_e/technical_symposium_2906_e.htm)); the WTO-WHO High-Level Dialogue on "Expanding COVID-19 vaccine manufacture to promote equitable access", on 21 July 2021 ([https://www.wto.org/english/news\\_e/spno\\_e/spno12\\_e.htm](https://www.wto.org/english/news_e/spno_e/spno12_e.htm)); and the High-Level Consultations of the Multilateral Leaders Task Force on COVID-19 with CEOs of vaccine manufacturing companies, 16 September 2021. ([https://www.wto.org/english/news\\_e/news21\\_e/covid\\_16sep21\\_e.htm](https://www.wto.org/english/news_e/news21_e/covid_16sep21_e.htm)).

## 2. TRADE-RELATED BOTTLENECKS

The following trade-related bottlenecks were identified by stakeholders at various events and consultations convened by the WTO, together with vaccine manufacturers in the context of the Multilateral Leaders Task Force on COVID-19<sup>6</sup>. They are compiled in categories for ease of reference. Entries under each section are presented in no particular order, and no judgement is made on the effect or significance of the reported bottlenecks.

### 2.1. Bottlenecks in the cross-border movement of vaccine inputs<sup>7</sup>

- Export restrictions (especially in large economies) continue to impede access to vaccine inputs and contribute to uncertainty on delivery timeframes by suppliers. They also continue to affect exports of finished vaccines and to hinder contributions to COVAX.
- Exports by vaccine manufacturers to foreign "fill and finish" sites can be subject to export restrictions, both for sites owned by the manufacturer and the contract development and manufacturing organizations (CDMOs) with which vaccine originators may have partnered.
- Export restrictions have impacted the conduct of clinical trials. The limited availability of reagents and equipment has reduced access to clinical assays required in clinical trials. These restrictions also impede the movement of critical biological samples from global clinical trials to centralized testing sites, resulting in delayed testing and results reporting.
- There is lack of predictability in the administration of import and export restrictions in some countries, which makes it difficult for vaccine manufacturers to plan and execute the sourcing of critical inputs.
- In response to these export restrictions, some countries have required local supplies of inputs, which has added further bottlenecks to regulatory approval, complexity to distribution planning and restrictions to vaccine availability in countries without extensive manufacturing infrastructure.
- Applied tariffs remain high for certain inputs in some manufacturing countries, which can have a cumulative effect on manufacturing cost, most notably on CDMOs in developing countries.
- Unlike finished vaccines and other essential products, vaccine inputs do not benefit from "green channels" and other simplified import, export and transit procedures, which include rigorous documentation requirements and frequent renewal of licences and certificates. Some national authorities adhere to a five-day working week, also observing bank holidays, which is sometimes insufficient to process the relevant paperwork effectively for the expeditious cross-border supply of the vaccine inputs.
- Non-commercial samples sent by vaccine manufacturers for testing and quality control purposes to specialized laboratories located abroad are subject to the same import and export procedures as commercial shipments, including export restrictions, which delays the quality control process and the release of lots for distribution.
- The importation of new equipment to scale up manufacturing or set up new production facilities in a country is subject to slow and sometimes difficult procedures.
- Some embassies and consulates remain closed as a result of lockdowns, making it impossible to complete consular transactions (sometimes referred to as legalization or consularization) or to submit documents needed for cross-border trade of vaccine inputs.

It is unclear whether these bottlenecks are faced by all vaccine manufacturers, and if all of them remain a problem as of the date of this information note. With respect to export restrictions, the information available in the WTO's Trade Monitoring Exercise suggests that at least 13 WTO

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<sup>6</sup> *Ibid.*

<sup>7</sup> Identifying the specific products that are used for vaccine manufacturing, as well as their tariff classification according to the World Customs Organization's (WCO) Harmonized System (HS), is a necessary first step for identifying the trade-related barriers that may be faced by these products. Together with other international organizations, researchers and some vaccine manufacturers, the WTO Secretariat prepared, in July 2021, the Joint Indicative List of Critical COVID-19 Vaccine Inputs for Consultation (Version 1.0), which is available at [https://www.wto.org/english/tratop\\_e/covid19\\_e/vaccine\\_inputs\\_report\\_e.pdf](https://www.wto.org/english/tratop_e/covid19_e/vaccine_inputs_report_e.pdf) and identifies 83 products for the manufacturing, distributing and administering of COVID-19 vaccines (e.g. active ingredients, inactive ingredients, flasks, vials, bags, instruments, equipment). The list also includes the possible HS classification based on an assessment by the WCO Secretariat, as well as reference to a recent decision by the Harmonized System Committee (HSC). However, it should be noted that some of those assessments have not yet been endorsed by the HSC and do not constitute official advice on their classification.

members maintain measures that may be affecting the exportation of certain inputs included in the Joint Indicative List of Critical COVID-19 Vaccine Inputs, and in particular some active ingredients that are classified in the HS together with the final vaccines under subheading 3002.20.

## **2.2. Bottlenecks stemming from vaccine regulatory approval**

- Differences between countries in terms of regulatory frameworks, procedures and timelines adds complexity for manufacturers and has created delays that range from several days to several weeks in the time it takes a manufacturer to deliver vaccines.
- Fora are needed to facilitate dialogue amongst manufacturers and regulators from different economies, which can reduce the time and resources required by manufacturers to provide the necessary information. A forum recently launched by stakeholders, including the European Medicines Agency, World Health Organization, and manufacturers to discuss needs for risk management plans (RMP) has proven to be helpful.

### **WHO Emergency Use Listing**

- There is a lack of expedited review procedures by some national regulatory authorities (NRAs) for vaccines granted WHO Emergency Use Listing (EUL/PQ). Some countries accepting WHO EUL/PQ products may have additional country-specific requirements, which adds complexity and time to the regulatory process.
- Inconsistent approaches and enforcement by governments in terms of accepting all vaccines granted WHO EUL/PQ as a basis for vaccine passports and travel exacerbate vaccine inequity and serve as a disincentive for vaccine manufacturers to set up broad networks of manufacturing sites across the world to ensure broad and equitable access.
- The process of granting WHO EUL/PQ could be accelerated for some vaccines. The review process for the approval of additional production lines by the WHO, including inspections, could be facilitated and expedited. While there has been recent progress, some delays persist in the WHO accepting EUL applications for certain regional supply chains that are not intended for global or regional supply through COVAX, the Pan American Health Organization (PAHO) or the United Nations Children's Fund (UNICEF), which creates challenges to donate vaccines produced at those facilities.

### **Application/registration and authorization/approval**

- Significant variation among application/registration regime requirements across different regions can make it onerous for manufacturers to apply for registration in multiple locations. Unique country specifications and requirements (e.g. labelling, risk management plans) are driving stock-keeping unit (SKU) variants and are limiting allocation flexibility of finished vaccines. For example, approval of diverse specifications in different regions adds complexity for planning supply chains and country donations. It also causes delays of several days to effectively prepare customized application information and concomitantly respond to queries associated with that customized content. Some countries require separate licences for each unique supply chain, if more than one supply chain is authorized for a given vaccine.
- For COVID-19 vaccines, while many NRAs have agreed to rely on the authorization and approval of stringent regulatory authorities (SRAs) (e.g. US Food and Drug Administration, European Medicines Agency), the lack of universal harmonization and reliance between many NRAs has resulted in duplicative procedures and delays in concurrent fillings and authorization/approval and ultimately delays of several days and interruptions in supply chain distribution while awaiting authorization/approval.
- Some NRAs have independently conducted complete reviews and have issued hundreds of queries, which can delay approval and divert critical resources. Confidential sharing of regulatory documentation and review outcomes from other NRAs (concerning the same regional supply chain) can help the local NRA to understand the scientific basis for the application under assessment, thereby accelerating the process.
- Local NRAs may require small bridging clinical trials, which can lead to delays. While this was generally not the case with COVID-19 vaccines, two NRAs initially requested local clinical trials to obtain authorization but ultimately waived that expectation, resulting in a delay of several months.
- Different technical requirements for the same product between countries (e.g. overfill requirements vary across countries; the sterilization of injectable products required by terminal sterilization in some countries versus by aseptic processing in other countries)

require manufacturers to establish separate production lines, which increases manufacturing cost and compromises access, affordability and speed of delivery, especially for low volume products. The delays are incurred not only from the need to develop separate/customized technical data to meet individual regulatory expectations but also during the regulatory assessment review and iterative query/response. Cumulatively, the delays can be in the range of two to four weeks.

### **Inspection**

- The use of remote inspection (in response to pandemic travel restrictions) has led some NRAs to request additional information on good manufacturing practices (GMPs) beyond what would normally be required. NRAs are requesting the same additional GMP information in an uncoordinated manner, resulting in duplication and wasted resources.
- There is a need for streamlined and expeditious inspection and approval of factories to facilitate partnerships and technology transfer to scale up production.

### **Release**

- Some NRAs require local retesting of vaccines by the official medicines control laboratory (instead of reliance on the releasing country), which adds steps to release processes and can lead to delays and reduce time remaining prior to expiration by as much as two weeks. The same batch of vaccines can be shipped to several countries, and therefore it may be tested for release a multiple of times by various countries.
- In some countries, limited testing capabilities and a scarcity of testing and reference materials has created additional barriers to product release.

### **Post-approval changes**

- The rapid development of COVID-19 vaccines has led to additional critical challenges and burdens for vaccine manufacturers following the initial emergency use authorization (EUA), such as gathering data and optimizing processes.
- Some NRAs have not established accelerated pathways or regulatory reliance procedures for post-approval changes to vaccines under EUA, for instance for the substitution of critical components, and other NRAs may require prior approval for all changes, regardless of the risk incurred. These reviews could hinder availability owing to delays in approval and supply interruption. Some NRAs which have reliance policies in place for post-approval variations have nevertheless requested additional Controls, Manufacturing and Chemistry (CMC) information over and above what was supplied to the reference NRA. The process for approval of new testing sites on account of post-approval changes is onerous and causes delays.

### **Donations**

- Because COVID-19 vaccines have a short shelf-life (between six and nine months in most cases), last minute decisions by donors often result in insufficient lead times for planning donations from a regulatory and manufacturing standpoint. This impedes necessary coordination between manufacturers, COVAX and recipient countries.
- Some NRAs require the registration of vaccines donated through COVAX (or other mechanisms) where the supply chains are not originally approved for their market. This can include the need for additional EUA licences, additional data requests on the quality and safety of batches that have already been released and extensively validated, as well new site registrations. This can delay the donation process and put vaccine stock at risk through shelf-life expiration. The delays can vary from two days to two weeks depending on the NRA. However, most NRAs are willing to waive or reduce local requirements to expedite donated doses.
- Countries have different shelf-life requirements for donated doses, which can complicate the dose allocation process and create varying logistical challenges for dose delivery by manufacturers. Harmonization on shelf-life requirements and improved dialogue between manufacturers and international agencies can improve dose delivery through COVAX.
- Some donors indicate to manufacturers that a certain share of a donated batch be earmarked for specific recipient countries, which can create complexity in arranging multiple regulatory

approvals. Last minute changes in terms of prioritized recipient countries can lead to delays and even spoilage due to the short shelf-life of the vaccines.

- Regulatory capacity is limited in many recipient countries.
- Challenges in establishing infrastructure (e.g. local call centres) for reporting and responding to adverse events in recipient countries.
- Differences in labelling requirements between the donor and recipient country add complexity and delays due to the need to relabel.

### **EUA and regular approval**

- There can be uncertainty about when the EUA will expire and the accompanying processes to move to regular approval and registration of vaccines (including against new coronavirus variants). A particular concern is that statutory timelines, release protocols, and other data and legal requirements that apply under regular approval may delay access to vaccines. Uncoordinated approaches by NRAs for the move from EUA to regular approval risk delays for patients. At this point, there is uncertainty about the duration of an EUA within each country before a formal licence application is required. In several instances, the impact has been significant in extending the authorization/approval of changes and optimization required to expand the scope and scale of manufacturing and testing to increase supply chain volume.
- Some NRAs have multiple EUA for different supply nodes, which have been necessary for manufacturers to maximize supply chain flexibility but have added complexity and further uncertainty around regular approval.

### **Scaling up production**

- Ongoing scale-up, alternate material introduction and new supply-point introduction to increase global supply require significant regulatory filings. In general for COVID-19, while NRAs agreed to expedite assessments of these submissions to enable increased volume, occasional NRA capacity constraints resulted in short supply chain disruptions (of less than a week in most cases).
- Limited regulatory capacity (e.g. to ensure quality and safety, pharmacovigilance and liability regimes) of some countries limits options for partnerships to scale up production.

### **Other emerging issues**

- There is limited availability of vaccine vial monitors (VVMs), which are critical for deliveries to low-income countries. Currently, there is only one supplier of VVMs.
- There is uncertainty and the risk of divergent approaches between NRAs with regard to the approval of boosters. Approval of larger booster doses (i.e. full versus half-dose) by SRAs could contribute to global supply shortages. Divergent booster regimens risk exacerbating travel issues and concerns around vaccine passports.
- There is a lack of specific guidance from NRAs on the requirements for booster dose approval (e.g. trial participant size, length of safety follow-up), which may differ between homologous and heterologous boosting regimens.
- A move to single dose containers for COVID-19 vaccines (e.g. for booster campaigns) could accentuate supply chain pressures (i.e. lead to an insufficient availability of vials).
- There are growing concerns about shelf-life and expiration of the current stock of vaccine doses.
- There is uncertainty about liability regimes applying to "mix-and-match" approaches and what the expectations are about data to be evaluated by regulators.
- Clarification from regulators on the continued development of vaccines is needed as the COVID-19 landscape evolves. There is a lack of specific guidance from NRAs on the development of vaccines to address variants of concern, based on the use of evidence from an existing vaccine technology. For example, it is becoming increasingly challenging to conduct placebo-controlled trials, particularly in vulnerable populations like paediatrics, as much of the population is no longer seronegative. NRAs have different approaches to the use of placebo controls, which delays the development of variant vaccines. Additional guidance from regulators would provide needed clarity on manufacturer development strategies.
- The expectations on data for paediatric vaccines are unclear.

- Country readiness to receive large volumes of COVID-19 vaccine should be assessed, and measures should be put in place to strengthen systems and deployment plans where required. Sufficient space needs to be created in Expanded Program on Immunization (EPI) fridges for swift management and administration of vaccines with different temperature storage requirements.

### **2.3. Bottlenecks in the distribution of finished vaccines and immunization supplies**

- Few challenges in the distribution and border clearance of COVID-19 vaccines have been identified so far. COVID-19 vaccine shipments have frequently become media events, with deliveries often being received by high level officials or are sent through government channels. However, border clearance conditions for ancillary immunization products (e.g. syringes, refrigerators and other cold chain equipment) needed for administering vaccines can be quite different. As the number of doses of COVID-19 vaccine delivered worldwide grows, it is unclear whether these expedited border clearance processes will remain in place.
- In some cases, there are limited number of commercial flights available, especially to and from countries which lock down borders.
- Lower-middle-income and low-income economies will need to scale up cold chain capacity to ensure they can absorb higher volume shipments, in particular for ultra-cold storage. Access of warehousing and refrigeration service suppliers to maintain existing, and construct additional, cold storage is an emerging concern.

### **2.4. Bottlenecks in trade in pharmaceuticals**

- Post-approval change requirements vary across markets. NRAs request different process changes to approved products in an uncoordinated manner, which requires manufacturers to carry multiple manufacturing processes. This can lead some manufacturers to exit some markets, especially those in countries with low levels of consumption. The potential delays associated with unsynchronized authorization/approval of manufacturing changes/supply chain expansion and scale-up range anywhere from one day to two months.
- Some NRAs require local population-based studies for therapeutics with no evidence of ethnic pharmacokinetic differences, which increases the time required to bring the product to market.
- Applied tariffs and other taxes can remain high in many countries, thereby making it costly to import essential therapeutics to treat COVID-19 patients.

### **2.5. Bottlenecks in trade in diagnostics and other medical devices**

- Divergent regulations and barriers to accessing viral samples that are needed to develop effective diagnostic tests.
- Some NRAs may still require a consularized apostille of the original paper document to confirm information already provided to the NRA and available online.
- Duplication of rigorous local testing can lead to delays and uncertainty for suppliers.
- An unclear process for regulatory approval of diagnostics can lead to diagnostics of varying quality. Inefficient and overly complex regulatory systems slow down activation of clinical trials and hamper the adoption of results.

### **2.6. Other trade-related bottlenecks**

- Complicated visa entry requirements, limited flights and the consequences of health regulations on the openness of borders mean that highly qualified personnel (e.g. engineers in charge of installing/repairing complex machinery, staff involved in manufacturing, validation of works or technology transfer) can find it difficult to move across borders to support vaccine manufacturing or to set up new production facilities in other countries. The problem has been compounded by sanitary protocols (e.g. mandatory quarantine), which have slowed down their arrival and the beginning of work. Countries with manufacturing facilities should consider staff involved in these projects as essential workers to facilitate their entry and allow free movement.
- Duplication of standards and multiple authorities responsible for regulating medical goods can increase complexity and drive up costs, including for developing country CDMOs.

- A lack of coordination among border agencies can lead to unnecessary delays, in particular for transit through third countries.
- Many administrations recognize (international) transport workers as essential and have taken measures to expedite their border entry and exit. Difficulties remain, however, that could cascade through into manufacturing delays. The sanitary entry protocols developed by the International Civil Aviation Organization (ICAO), the International Road Transport Union (IRU), the WHO and other relevant bodies are pertinent in this context.
- A two-tier system of vaccine passports has emerged, with access to travel dependent on where the vaccine has been manufactured. This risks undermining confidence in vaccines and may disincentivize vaccine manufacturers to set up broad networks of manufacturing sites across the world.

### 3. POSSIBLE TRADE-FACILITATING MEASURES

The following suggestions were raised by stakeholders at various events and consultations convened by the WTO, including vaccine manufacturers in the context of the Multilateral Leaders Task Force on COVID-19<sup>8</sup>. They are compiled in categories for ease of reference. Entries under each subheading are presented in no particular order, and no judgement is made on the desirability of implementing any of these suggestions.

#### 3.1. General import, export and transit procedures

- Implementation of the provisions in the Trade Facilitation Agreement (TFA), such as those concerning pre-arrival procedures, could help to expedite the movement of essential products to combat COVID-19, as delays may have a detrimental impact on public health. Where possible, implementation of the provisions in the TFA should be accelerated.
- Enhanced cooperation among governments, international organizations and the private sector is critical to ensure that all relevant stakeholders have sufficient information to make decisions.
- Where possible, digitalization and simplification of import, export and transit procedures (e.g. paperless trade) should be accelerated.
- An examination of best practices by WTO members can help to identify solutions to bottlenecks and new trade-facilitating measures, which could further expedite trade in these products.<sup>9</sup> Where possible, existing tools and international standards can be used.
- Identification of relevant HS codes for medical goods essential for the treatment of COVID-19 by the WCO and the WHO greatly assists members and other stakeholders in identifying the relevant products in global trade and their tariff classification, and enables the establishment of expedited procedures for border clearance.
- Enhanced availability of custom authorities 24 hours a day, 7 days a week, allows for expeditious clearance procedures.

#### 3.2. Vaccine manufacturing and its inputs

- Transparent and predictable inward investment regimes can facilitate planning and executing vaccine and consumables production plans.
- Exemptions from export restrictions for critical materials and samples used for clinical and analytical testing could help expedite clinical testing and development of COVID-19 vaccines.

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<sup>8</sup> These include: WTO webinar Regulatory Cooperation during the COVID-19 Pandemic, on 2 June 2021, ([https://www.wto.org/english/news\\_e/news21\\_e/trip\\_28may21\\_e.htm](https://www.wto.org/english/news_e/news21_e/trip_28may21_e.htm)); the WTO symposium COVID-19 Vaccine Supply Chain and Regulatory Transparency, on 29 June 2021 ([https://www.wto.org/english/tratop\\_e/trips\\_e/technical\\_symposium\\_2906\\_e.htm](https://www.wto.org/english/tratop_e/trips_e/technical_symposium_2906_e.htm)); the WTO-WHO High-Level Dialogue on "Expanding COVID-19 vaccine manufacture to promote equitable access", on 21 July 2021 ([https://www.wto.org/english/news\\_e/spno\\_e/spno12\\_e.htm](https://www.wto.org/english/news_e/spno_e/spno12_e.htm)); and Multilateral Leaders Task Force on COVID-19 consultations with CEOs of vaccine manufacturing companies, 16 September 2021 ([https://www.wto.org/english/news\\_e/news21\\_e/covid\\_16sep21\\_e.htm](https://www.wto.org/english/news_e/news21_e/covid_16sep21_e.htm)).

<sup>9</sup> Information on trade-facilitating measures taken by some members is available on the WTO TFA Database: see <https://tfadatabase.org/trade-facilitation-committee/experience-sharing>. Information on regulatory measures adopted and notified by WTO members in response to the pandemic, including temporary streamlining of conformity assessment procedures, is available at [https://www.wto.org/english/tratop\\_e/covid19\\_e/standards\\_report\\_e.pdf](https://www.wto.org/english/tratop_e/covid19_e/standards_report_e.pdf).

- Bilateral and regional agreements could ease import and export restrictions on input supplies of key routes, but requirements for NRA registration approvals should be considered and potentially waived in emergency circumstances.
- To obtain clear and reliable information, a communication channel can be established between vaccine manufacturers and other relevant stakeholders to raise awareness about bottlenecks at domestic and regional levels (e.g. with a national committee on trade facilitation).
- Dialogues at the domestic level with manufacturers and other relevant stakeholders could be established to understand the current conditions for trade in critical vaccine inputs.
- Predictable tariff classification in the HS is in itself a trade-facilitating measure, but it may not be sufficiently clear for the wide range of critical inputs used in vaccine manufacturing. Members could engage in the WCO Harmonized System Committee to identify the relevant products and to agree on the appropriate classification.
- Consider the creation of a global "watch tower" (e.g. a market information system) to increase transparency and to highlight pinch points on the availability of inputs globally.
- Measures to increase consumables capacity should be further explored.

### **3.3. Vaccine regulatory approval**

#### **Dialogue and cooperation**

- Constant and early dialogue between vaccine manufacturers and NRAs and the WHO is essential to exchange information and to accelerate the different procedures. Some countries have established mechanisms to meet weekly or even daily, which has greatly enhanced coordination and accelerated the approval process.
- As the COVID-19 landscape evolves, countries have modified their regulatory pathways at different rates. Consistency in feedback provided by NRAs to manufacturers will help streamline regulatory pathways and responses from manufacturers.
- Early and concerted dialogue between NRAs of different countries can help to align expectations and to promote reliance and recognition.
- A global or multilateral forum could be considered for regulators to meet with manufacturers and exchange information on COVID-19 vaccines.

#### **Application/registration and authorization/approval**

- The promotion of harmonization and reliance among NRAs can accelerate access to COVID-19 vaccines. In a pandemic, there could be automatic recognition of approvals (and associated recognition of manufacturing facilities) if already approved by one of the WHO-recognized SRAs.
- NRAs could facilitate an EUA based on the WHO Emergency Use Listing or approval by WHO-recognized SRAs (e.g. WHO prequalification collaborative registration procedure, SRA collaborative registration procedure) and regional networks (e.g. African Medicines Regulatory Harmonization (AMRH) initiative, harmonized requirements for drug registration of the Association of Southeast Asian Nations). WHO special procedures can be used to share regulatory dossiers under confidentiality agreements and to promote the use of reliance to allow low-income and middle-income countries to authorize emergency use of vaccines quickly and efficiently.
- NRAs could activate (or create) national EUA pathways. Authorization of COVID-19 vaccines could be fast tracked. For vaccines granted WHO EUL/PQ, there could be an expedited review procedure for granting EUA based on reliance on WHO EUL/PQ.
- NRAs can allow restricted emergency use of foreign-produced vaccines with EUA by SRAs, under the condition of post-approval Real-World Data/Evidence (RWD/RWE) or a bridging trial.
- Rapid approval of clinical trials (phases undertaken in parallel in real-time) could expedite approval of vaccines.
- A rolling review of vaccine and therapeutics dossiers can shorten approval time.
- Confidential sharing of regulatory documentation and review outcomes from other NRAs as part of the country-specific application (concerning the same regional supply chain) can help the local NRA to understand the scientific basis for the application to speed the review. However, efforts should be made to avoid duplicative queries and inefficient use of resources by regulators and industry in this context.



## Inspection

- Mutual reliance or recognition of remote GMP inspections could be encouraged.

## Release

- Where appropriate, batch release testing from NRAs or national control laboratories of the releasing country (through the WHO-National Control Laboratory Network for Biologicals) could be relied upon.

## Flexibilities

- NRAs can speed up approval of new production sites for COVID-19 vaccines and their inputs by relaxing or waiving the usual application requirements and timelines.
- NRAs can relax or waive requirements for separate licences for each unique supply chain if more than one is authorized for a given vaccine.
- NRAs can allow for e-labelling (i.e. standardized English packaging with a QR code that links to relevant label and leaflet information in the local language). This avoids country-unique labelling and packaging and the need to print paper leaflets.
- NRAs can consider accepting production coming from both EUL certified production lines and non-EUL certified production lines while these lines await WHO approval.
- In case agile inspections cannot be conducted, appropriate alternatives could be found (e.g. through remote means).

## Post-approval changes

- Scientific advice from NRAs could be made publicly available to developers and manufactures to speed up development of COVID-19 vaccines and save resources. This is especially relevant for post-approval changes that may be required to cater for variants.
- There is a need for facilitated processes and protocols for post-approval changes that may be required to cater for variants as the pandemic progresses.

## Surveillance

- Greater use of reliance and work sharing for quality, safety and vigilance could be encouraged. For example the WHO *COVID-19 Vaccines: Safety Surveillance Manual*<sup>10</sup> recommends, among other things, regulatory reliance.

## Transparency

- Building transparency by design – for all parties, including regulators and manufacturers – could enable agile and informed regulatory decision-making during a pandemic and strengthen collaboration for more efficient vaccine development.
- NRAs can enhance transparency and openness (e.g. sharing data nationally with experts and explaining the process and findings at public briefings) and gather independent expert advice in real-time to mitigate any potential risks of expedited processes.
- Further information sharing between NRAs can promote regulatory alignment on the questions received by manufacturers. For example, the ACCESS Consortium, which includes the UK Medicines & Healthcare products Regulatory Agency (MHRA), Health Canada, the Therapeutic Goods Administration (TGA) Australia, the Health Sciences Authority (HSA) Singapore, and the Swiss Agency for Therapeutic Products (Swissmedic), allows for improved sharing of information.
- The pharmaceutical industry could improve transparency and data integrity by providing better access to clinical data for all new medicines and vaccines (including to the approximately 50% of clinical trials that go unreported because the results are negative<sup>11</sup>).

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<sup>10</sup> See <https://apps.who.int/iris/handle/10665/338400>.

<sup>11</sup> See [https://www.who.int/news/item/07-05-2021-joint-statement-on-transparency-and-data-integrity-international-coalition-of-medicines-regulatory-authorities-\(icmra\)-and-who](https://www.who.int/news/item/07-05-2021-joint-statement-on-transparency-and-data-integrity-international-coalition-of-medicines-regulatory-authorities-(icmra)-and-who).

### Scaling up production

- Regulatory systems in developing countries can be strengthened to enable or scale up the local manufacture of vaccines.

### Donations

- Donors could provide earlier indication of their intention to donate (and clarity on recipients in case of earmarked donations) to enable better coordination and to facilitate necessary regulatory and manufacturing arrangements.
- It may be more efficient to process a small number of donations involving a larger quantity of vaccines than to process many donations involving relatively small volumes.
- Coordination between manufacturers, COVAX and recipient countries can be improved.
- NRAs, in cooperation with manufacturers, can consider extending the shelf-life of specific batches of vaccines to facilitate the donation process.

### Other emerging issues

- The use and acceptance of RWD/RWE by regulators can be promoted for regular vaccine approval and post-approval changes. NRAs are not currently aligned or experienced in using RWD/RWE. Vaccines offer a good platform to leverage this opportunity, which is also relevant for other medical products.
- Enhancing cooperation on mix-and-match approaches can help to alleviate supply and booster challenges.

### 3.4. Pharmaceuticals

- Global harmonization with guidelines set by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) (e.g. guidelines on pharmaceutical development (Q8), on specifications (Q6), on impurities (Q3) and on stability (Q1)) would allow pharmaceuticals to be developed faster and to move more quickly between countries by overcoming conflicting or varying pharmacopeia requirements.

### 3.5. Diagnostics and medical devices

- The Medical Device Single Audit Program of the International Medical Device Regulators Forum (IMDRF) could be used to overcome barriers to on-site inspection during a pandemic.
- The IMDRF could establish guidance for the regulatory flexibility needed during a pandemic.
- The WHO provides recommendations in *Global Model Regulatory Frameworks and Regulatory Reliance for Medical Devices*.
- NRAs could implement a good regulatory practice (GRP) policy and related standard operating procedures.
- WHO guidance on recognition and reliance for pre- and post-market activities could be implemented.
- National standards and conformity assessment procedures (based on international standards) could be developed for local manufacturing of PPE.
- A common international regulatory framework that better defines criteria for effectiveness, quality and use cases for diagnostics should be developed. SRAs could work together to develop international assessment protocols and guiding principles in addition to more effective quality assurance processes.
- The streamlining of existing EUA pathways in the context of pandemics could result in diagnostics being registered and made accessible with less delay.
- Sharing best practices and data could mitigate delays and reduce uncertainty.
- Multiple-source supply chains can ensure that trade flows as freely as possible and with the minimal of export restrictions. A delay in the shipment of a single component, which might not be classified as a medical product in itself, could halt the entire production in a factory. Multiple-source supply chains allow manufacturers to respond to unanticipated spikes in demand. The reliance on multiple-source supply chains underscores the need for policymakers to commit to reducing trade restrictions.

### 3.6. General regulatory aspects

- Mutual recognition agreements could be promoted, as well as the recognition of marketing authorization procedures and the unilateral recognition of marketing authorizations. Recognition of GMP inspections (e.g. Pharmaceutical Inspection Co-operation Scheme (PIC/S)) could help to avoid duplication, and inspections could be further harmonized through enhanced cooperation between regulators (building on PIC/S) to address country-specific requirements, thereby reducing burdens.
- Encouraging the sharing of regulatory workflows, data and review information could accelerate access to essential medical goods.
- The use of existing cooperation arrangements and guidelines (e.g. ICH, IMDRF, PIC/S, International Coalition of Medicines Regulatory Authorities (ICMRA)) could be strengthened to improve preparedness for future pandemics.
- Global alignment of clinical trial requirements (e.g. patient versus healthy volunteer studies, crossover study versus parallel study, different end points) can increase the pace at which vaccines, therapeutics and diagnostics can be developed.
- Timelines for the evaluation and approval of medical products and clinical trials could be shortened accordingly if approval has already been granted by trusted NRAs.
- Transparency could be enhanced by providing the public with regularly updated information online on regulatory decisions and processes.