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International Trends in Responses to the COVID-19 Pandemic in the Pharmaceutical Sector

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Food, Drugs, and Devices

This Alert discusses relevant mechanisms and cross-border trends in responding to the COVID-19 pandemic in the pharmaceutical sector. It focuses on international developments and does not consider the many initiatives and activities that are taking place at the national or local level.

World Health Organisation

A. Access to COVID-19 Tools Accelerator

Following a recent United Nations ("UN") General Assembly Resolution on "International Cooperation to ensure global access to medicines, vaccines and medical equipment to face COVID-19",[1] the World Health Organization ("WHO") announced the launch of a global partnership between public health bodies and private stakeholders to accelerate the development, production and equitable global access to new COVID-19-essential health technologies.[2] The so-called Access to COVID-19 Tools ('ACT') Accelerator ("ACT Accelerator") will serve as a platform to coordinate and align government policies and industry efforts in order to obtain safe and affordable treatments for COVID-19 swiftly.

Eleven countries participated in the ACT Accelerator launch, including France, the United Kingdom ("UK") and South Africa. The initial group of participants also includes a number of other public and private stakeholders.

B. WHO Emergency Use Listing

Beyond specific COVID-19-related initiatives, the WHO also operates a so-called Emergency Use Listing ("EUL") procedure,[3] which is largely intended to facilitate supply of unlicensed medicines in emergency situations. It was initially developed in response to the 2014-2016 Ebola outbreak. The purpose of an EUL is to assist UN procurement agencies, *e.g.*, the UN's

[1] *See* https://www.un.org/pga/74/2020/04/20/international-cooperation-to-ensure-global-access-to-medicines-vaccines-and-medical-equipment-to-face-covid-19-2/.
[2] *See* https://www.who.int/news-room/detail/24-04-2020-global-leaders-unite-to-ensure-everyone-everywhere-can-access-new-vaccines-tests-and-treatments-for-covid-19.
[3] *See* https://www.who.int/diagnostics_laboratory/eual/procedure/en/

children's emergency fund UNICEF and WHO Member States, by confirming the acceptability of an unlicensed medicine, an *in-vitro* diagnostic product ("IVD") or a vaccine for use in a public health emergency, based on an evaluation of a limited set of quality, safety, and efficacy data.

The WHO EUL is a time-limited listing, and a manufacturer would be expected to complete product development and apply to the WHO's prequalification scheme to be included on the list of essential medicines. In other words, a listing is not a substitute for seeking a marketing authorisation in any of the WHO members states. That said, the WHO EUL may be a helpful tool if a company intends to place its products on the market in countries where regulators have difficulty coping, or through UN procurement agencies.

To obtain a WHO EUL, it is very helpful to have an (emergency) approval in the U.S. or the EU. It is also possible to pursue these in parallel to the WHO EUL, and coordinate the processes. The WHO would not duplicate the work of the U.S. Food and Drug Administration ("FDA") or the European Medicines Agency ("EMA"), and it can implement a tailored, abridged procedure with the U.S. or European Union ("EU") serving as a reference.

As of 24 April 2020, there have been four IVDs that have been listed,[4] following the invitation issued by the WHO on 28 February 2020 to manufacturers of IVDs.

European Union

A. Tariff Liberalisation for Medical Equipment

In early April 2020, the European Commission published a Decision on relief from import duties and VAT exemption on the import of medical equipment needed in response to the COVID-19 pandemic.[5]

Subsequently, the EU's Commissioner for Trade, Phil Hogan, announced that, in light of the current crisis, the EU was contemplating a range of other trade measures. Among others, he suggested that countries should consider negotiating a plurilateral agreement, which could provide for a permanent liberalisation of tariffs on medical equipment. He cautioned that such proposals would require further analysis and deliberation within the European Commission before more concrete measures could be taken.[6]

B. Risk of Product Shortages

1. Overview

A number of health service providers across EU Member States have been anxious to source medicinal products to help address the COVID-19 crisis, either to treat COVID-19 patients, related medical conditions, or even to respond to changes in the way the health service treats patients who are unaffected with COVID-19 but who can no longer go to hospitals. This has led

[4] *See* https://www.who.int/diagnostics_laboratory/200424_eul_sars_cov2_product_list.pdf?ua=1.
[5] *See* https://ec.europa.eu/taxation_customs/sites/taxation/files/03-04-2020-import-duties-vat-exemptions-on-importation-covid-19.pdf.
[6] *See* https://ec.europa.eu/commission/commissioners/2019-2024/hogan/announcements/introductory-statement-commissioner-phil-hogan-informal-meeting-eu-trade-ministers_en.

to a significant increase in demand for certain products, including anaesthetics, antibiotics, and muscle relaxants, as well as medicines used off-label for COVID-19.

Such an increase in demand brings with it the risk of shortages in supply. In the EU, marketing authorisation holders ("MAHs") and wholesalers of medicinal products are under an obligation to ensure appropriate and continued supply of medicines actually placed on the market in a Member State. Indeed, companies are required to notify relevant national competent authorities if a product ceases to be placed on the market of a Member State, either temporarily or permanently.

While these obligations exist at the national level, the EMA recently announced that it was taking steps to support the availability of critical medicines used in the COVID-19 pandemic.[7]

An EU Executive Steering Group on Shortages of Medicines Caused by Major Events will coordinate action on shortages within the EU and is collaborating with industry to establish the i-SPOC (industry single point of contact) system, to fast-track interaction on shortages with the EU Executive Steering Group. Companies will report directly to EMA anticipated shortages of COVID-19 critical medicines. The system will run in parallel with existing mechanisms for reporting such shortages to national competent authorities.

At the national level, a number of Member States have also taken measures to counteract any potential shortages of such critical products. For example, Belgium has adopted measures, which allow the regulators to requisition and reallocate products and to impose export controls within and outside of the EEA. Similarly, the French Government has banned the export of hydroxychloroquine and lopinavir/ritonavir. In Italy, the regulator is engaging with the Italian trade association on a more informal basis with a view to managing any potential shortages.

2. Relaxation of Regulatory Requirements to avoid Product Shortages

The European Commission, the EMA and the Heads of Medicines Agencies ("HMA") have published a Notice to Stakeholders, which seeks to assist MAHs by providing guidance on regulatory expectations and flexibility during the COVID-19 pandemic.[8] This includes scope for a "0 day" mutual recognition process whereby products approved in one EU Member State can gain rapid approval in others, as well as flexibility to use product labelled for particular Member States more widely. Importantly, the Notice sets out details on the new exceptional change management process ("ECMP") for supply chains that is available to MAHs of products that are "*crucial medicines for use in COVID-19 patients.*"

Specifically, the procedure allows an MAH to make exceptional changes to its supply chain, if this is necessary to avoid shortages, and without the need to vary the marketing authorisation in advance. Potential changes include, for example, sourcing starting materials, reagents, intermediates and active substances from suppliers not listed on the marketing authorisations or to use manufacturing sites or sites responsible for quality control that are not specifically listed in the marketing authorisation. The ECMP is subject to certain conditions, including that any adjustments do not impact the quality of the medicinal product, *i.e.*, manufacturing must comply

[7] *See* https://www.ema.europa.eu/en/news/eu-actions-support-availability-medicines-during-covid-19-pandemic-update-2.
[8] *See* https://ec.europa.eu/health/sites/health/files/human-use/docs/guidance_regulatory_covid19_en.pdf.

with approved specifications and processes. Any new sites must also have a valid GMP certificate, either issued by an EU competent authority or an authority of a country, with which the EU has a mutual recognition agreement.

If a company intends to rely on the ECMP procedure, it must notify the relevant national competent authorities or, for centrally-authorised products, the EMA within 48 hours of implementing the change. The MAH must commit to submit the relevant variation applications within six months of implementing the change.

C. National Procurement in Emergency Situations

As demand for certain products increases, public authorities in the EU are facing difficulty on how to reconcile the need for speedy supply of products with their obligations under EU public procurement rules. In the normal course, public authorities (including, among others, government departments, local authorities and health service providers) in the EU must procure goods and services in accordance with the EU Public Procurement Directive 2014/24/EU, where the contract value exceeds certain thresholds. Tender processes under the EU procurement regime are often complex and time-consuming, which is difficult to reconcile with the need for a timely response to the current pandemic.

The EU Public Procurement Directive provides some leeway for procurement exercises in emergency situations. To that end, the European Commission has recently issued Guidance on using the public procurement framework in the COVID-19 crisis.[9] The Guidance recognizes the need for Member State authorities to respond to the pandemic promptly. It therefore encourages authorities to rely on digital tools to facilitate the procurement process. The Guidance also highlights the specific mechanisms under the Public Procurement Directive, which allow for shorter timelines for certain tender processes in case of urgency or extreme urgency. The Guidance also acknowledges that in certain circumstances, it may be necessary on grounds of extreme urgency to award a contract directly to one or more specific suppliers, provided that such awards only cover gaps until "*more stable solutions can be found.*" Thus, authorities cannot rely on urgency to procure products for routine, long-term use.

D. EU Joint Procurement Agreement

In addition to national procurement initiatives, a large number of Member States have recently relied on the EU Joint Procurement Agreement ("JPA")[10] to collectively procure personal protective equipment ("PPE") in response to the COVID-19 pandemic. The JPA was developed as part of the "*lessons learnt from the A/H1N1 pandemic*" in 2010. Currently, all EU Member States, Norway, Iceland, and Bosnia and Herzegovina are Contracting Parties to the JPA. It allows the European Commission to co-ordinate procurement processes for "medical countermeasures" ("MCMs") across at least four Contracting Parties. The concept of MCMs is broad, and includes medicines, medical devices, and other goods or services aimed to combat "*serious cross-border threats to health*," such as communicable diseases.

Participation in a joint procurement initiative is voluntary. Contracting Parties may participate in a joint procurement initiative under the JPA but remain free to conduct their own tender

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[9] *See* https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52020XC0401(05)&from=EN.
[10] *See* https://ec.europa.eu/health/preparedness_response/joint_procurement_en.

processes. The JPA also provides for certain mechanisms that regulate the allocation of goods across the participating Contracting Parties. While the European Commission coordinates efforts under the JPA, any contractual arrangements are directly with the participating Contracting Parties.

So far, this joint procurement procedure has only been used to procure PPE equipment to date. That said, there have been reports on the European Commission and certain Contracting Parties recently considering relying on the JPA to procure medicinal products that have shown some promising results in the treatment of COVID-19 patients.

There has also been some controversy about the UK not joining in the joint procurement initiative for PPE. The European Commission had confirmed at the time that the UK was welcome to join. Some voices suggested that the UK Government refused to join for political reasons so as not to undermine its position in the Brexit negotiations. Senior individuals in Government rejected these arguments and pointed to a delay in communications as the reason for the UK not joining the initiative.

E. European Medicines Agency's Incentives for Developing Medical Countermeasure

The EMA encourages developers of potential COVID-19 vaccines or treatments to make contact *via* 2019-ncov@ema.europa.eu as soon as possible to discuss their proposal and strategy for generating evidence.[11] Following an initial discussion, the EMA may consider a number of possible options to accelerate development and approval, including:

- scientific advice, which may be free of charge or fast-tracked;
- the PRIME scheme;[12] and
- the accelerated assessment and conditional MA procedures.

The EMA is currently engaging with developers of several potential treatments and vaccines for COVID-19.

F. Clinical Trials

The EMA, the HMA and the European Commission published Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic ("Guidance").[13]

The Guidance provides information on changes and protocol deviations that may be needed in the conduct of clinical trials during the COVID-19 pandemic. This may include quarantines, site

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[11] *See* https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/guidance-medicine-developers-companies-covid-19.
[12] PRIME is a scheme launched by the EMA to enhance support for the development of medicines that target an unmet medical need. This voluntary scheme is based on enhanced interaction and early dialogue with developers of promising medicines, to optimize development plans and speed up evaluation so these medicines can reach patients earlier. *See* https://www.ema.europa.eu/en/human-regulatory/research-development/prime-priority-medicines.
[13] *See* https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf?utm_source=POLITICO.EU&utm_campaign=bc6c97e2e3-EMAIL_CAMPAIGN_2020_04_28_12_07&utm_medium=email&utm_term=0_10959edeb5-bc6c97e2e3-190028305.

closures, travel limitations, and supply chain interruptions. The Guidance includes a harmonized set of EU-level recommendations to ensure the safety of trial participants while preserving data integrity. To that end, sponsors and investigators should base any decision to adjust the conduct of a trial on a documented risk assessment and implement measures that prioritize subject safety and data integrity.

As clinical trials in the EU are authorized at the national level, the Guidance encourages Member States to implement its recommendations "*to the maximum possible extent*" and to add to the Guidance where clarity on national legislation and derogations is needed. The Guidance also advises how these changes should be notified to national authorities.

The EMA's recommendations for potential changes include for example:

- Changes to reduce the number of site visits. Moreover, sponsors and investigators may have to consider changes to communication between more generally the trial sites and trial participants, including in relation to patient monitoring and safety reporting. Phone calls and/or telemedicine/ video visits may need to be considered.
- Changes to the distribution of the Investigational Medicinal Product ("IMP") to ensure patients receive treatment and avoid unnecessary physical site visits. This could be achieved for example by storing larger amounts of IMP at the site, making larger amounts of IMP available to trial participants, delivering IMP to trial participants' homes directly, and even, in exceptional cases, permitting distributors to deliver to trial participants directly in order to alleviate the sponsors' increased burden of IMP shipments.

At a national level, Ireland recently announced that it will fast-track the review of COVID-19 applications for clinical trials and clinical investigations. To that end, the Irish Minister of Health also intends to set up a dedicated COVID-19 ethics committee.[14] On April 22, 2020, the German Paul-Ehrlich-Institute approved a combined phase I and II trial for four COVID-19 vaccine candidates. Another trial at the University of Oxford in the UK has started on April 23, 2020.

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[14] *See* https://www.hpra.ie/homepage/medicines/news-events/item?t=/covid-19-related-human-research-expedited-regulatory-and-ethical-review&id=fe5c0d26-9782-6eee-9b55-ff00008c97d0.