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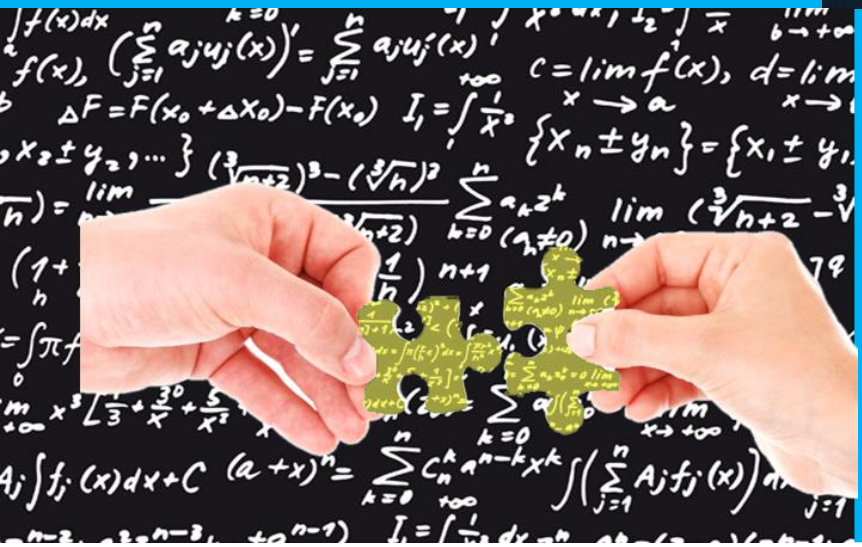
Regulatory Cooperation in Vaccines in the Asia-Pacific Region



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ASIA-PACIFIC RESEARCH AND TRAINING NETWORK ON TRADE

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ASIA-PACIFIC RESEARCH AND TRAINING NETWORK ON TRADE

WORKING PAPER

Regulatory Cooperation in Vaccines in the Asia-Pacific Region

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Abstract

The global health crisis that came to be known as the COVID-19 pandemic and started to sweep across the world in early 2020 revealed many vulnerabilities in the economic, social, and political fabric underpinning what much of the world had come to accept as normal. In ways that we are still grappling to understand, the pandemic and the many disruptions it brought about have ushered in significant changes to the way we work, consume, spend our leisure time, and even our relationships to government. In many ways, the pandemic has wrought a significant realignment between citizens and governments, both in terms of the expectations the former have of the latter and the powers the latter claims and exerts over the former. This paper explores the ways in which medicines (of which vaccines are a subset) are regulated today and what goals governments generally pursue in this policy area. It then turns to an examination of international regulatory cooperation in medicines before examining the unprecedented levels of international cooperation seen in response to the COVID-19 pandemic between not only governments but also the private sector and non-governmental organizations. The paper seeks to elucidate the regulatory cooperation in the area of vaccines that took place during the COVID-19 pandemic in the Asia-Pacific and concludes by discussing the present outlook while also setting out some policy recommendations for governments going forward.

Keywords: COVID-19, vaccines, regulatory cooperation, regional cooperation, Asia-Pacific

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List of abbreviations

ADB	Asian Development Bank
ADRs	Adverse Drug Reactions
APVAX	Asia Pacific Vaccine Access Facility (ADB)
APEC	Asia Pacific Economic Cooperation
ASEAN	Association of South East Asian Nations
CARES	COVID-19 Active Response and Expenditure Support Program (ADB)
CDER	Center for Drug Evaluation and Research (U.S. FDA)
CHMP	Committee for Medicinal Products for Human Use (EU)
CPMP	Committee for Proprietary Medicinal Products (EU - superseded)
DCGI	Drugs Controller General of India
eCTD	Electronic Common Technical Document
ESCAP	Economic and Social Commission for Asia and the Pacific (UN)
FDA	Food and Drug Administration (USA)
FD&C Act	Federal Food, Drug, and Cosmetic Act
EMA	European Medicines Agency
GCP	Good clinical practice
GLP	Good laboratory practice
GMP	Good manufacturing practice
GPvP	Good pharmacovigilance practice
ICMRA	International Coalition of Medical Regulatory Authorities
IPC	Infection prevention and control

IND	Investigational New Drug (U.S. FDA)
JACG	Joint Assessment Coordination Group (ASEAN)
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency (UK)
MSA	Medical Sciences Authority (Singapore)
NASEM	National Academies of Sciences, Engineering, and Medicine (U.S.)
NDA	New Drug Application (U.S. FDA)
NMPA	National Medical Products Administration of the State Council (China)
NRA	National drug regulatory authorities
PMS	Post-marketing surveillance
PPE	Personal protective equipment
PPWG	Pharmaceutical Products Working Group (ASEAN)
RAG	Regulatory Advisory Group (within COVAX)
SEARN	South East Asian Regulators Network (WHO)
SII	Serum Institute of India
SME	Small and Medium Sized Enterprise
SRA	Stringent Regulatory Authority
TGA	Therapeutic Goods Administration (Australia)
UN	United Nations
VTF	Vaccine Task Force (India)
WHO	World Health Organization
WTO	World Trade Organization

Introduction

The global health crisis that came to be known as the COVID-19 pandemic, and which started to sweep across the world in early 2020 shows no signs of abating at the time of writing (April 2022), due to the emergence of new variants and resulting fresh outbreaks in places that had previously been deemed to have vanquished the virus, such as the Peoples Republic of China. The pandemic revealed many vulnerabilities in the economic, social, and political fabric underpinning what much of the world had come to accept as normal. In ways that we are still grappling to understand (since the dust has not yet completely settled), the pandemic and the many disruptions it brought about, have ushered in significant changes to the way we work, consume, spend our leisure time, and even our relationships to government. In many ways, the pandemic has wrought a significant realignment between citizens and governments, both in terms of the expectations the former have of the latter and the powers the latter claims and exerts over the former (Brown, Brechenmacher and Carothers, 2020).

After first framing the discussion and delimiting the paper's scope in **Section 1**, this contribution then turns its focus to a general discussion of the ways in which medicines (of which vaccines are a subset) are regulated today and what goals governments generally pursue in this policy area - **Section 2**. Next the paper turns to an examination of international regulatory cooperation in medicines - **Section 3**. **Section 4** then discusses the unprecedented levels of international cooperation seen in response to the COVID-19 pandemic between not only governments but also the private sector and non-governmental organizations, before **Section 5** then turns to an examination of regulatory cooperation in the area of vaccines in the Asia-Pacific. Finally**, Section 6** discusses the present outlook while also setting out some policy recommendations for governments going forward.

Throughout our research, although we took into consideration efforts and initiatives at the global level, we focused our attention on the experiences of governments and other actors in and as they relate to the **following regional economies**:

1. India
2. Peoples' Republic of China
3. Singapore
4. Cambodia
5. Vietnam
6. Bangladesh
7. Vanuatu
8. Australia

This selection was made because it represents a fair sample of different-sized regional economies at varying degrees of economic development and at various removes from the global vaccine supply chain (discussed in another contribution to this series).

Throughout the paper, we present a number of case studies on how each of these economies dealt with the pandemic, its economic impact and the race to produce or procure and then rollout vaccines.

An annex to this report contains a Future Preparedness Regulatory and Policy Benchmarking Tool to guide policymakers and political leaders in future efforts at improving the regulatory structures and processes discussed in this paper.

1. Framing the Discussion

This paper explores the massive strides that were made in response to the COVID-19 pandemic by national drug regulatory agencies (NRAs) in order to achieve what ultimately became the fastest incidence in human history of the development, testing, approval, manufacture, and distribution of a new vaccine to an infectious respiratory disease that at the time of writing has by some estimates claimed over 6 million human lives.[3] Our purpose in writing this paper is to highlight what regulators did right, where the pandemic shone a light on gaps, and what can be done by national governments to increase readiness in their NRAs for the next time they are called upon to execute their role in a similar herculean effort.

1.1 International Regulatory Cooperation in Vaccines Part of a Broader Dynamic

International regulatory cooperation in vaccines is but a small part of international regulatory cooperation in the area of medicines. However, its importance has been thrust to center stage recently as a result of the COVID-19 pandemic with governments all over the world moving at breakneck speed to inoculate their populations with a completely new generation of vaccines, in some cases based on revolutionary new technologies.[4] Because it is embedded in the broader processes of international cooperation between national authorities tasked with the approval of new medicines, namely NRAs, our discussion of this subject is likewise inevitably framed within the wider structures that characterize international regulatory cooperation in medicines, of which vaccines are but a subset.[5]

[3] This figure from Our World in Data, last updated per the end of April 2022.

[4] This was the case with a number of vaccines based on so-called mRNA technologies. See, among many, Dolgin 2021.

[5] The Australian Therapeutic Goods Administration (TGA) describes vaccines as "medicines that protect you against specific diseases" (https://www.tga.gov.au/vaccines-overview) whereas the US Food and Drug Administration (FDA) offers several definitions of what comprises a drug, including "a substance intended for use in the diagnosis, cure, mitigation, treatment, or **prevention** of disease (emphasis added - https://www.fda.gov/drugs/drug-approvals-and-databases/drugsfda-glossary-terms). The European Medicines Agency (EMA) for its part, defines a medicinal product as "a substance or combination of substances that is intended to treat, **prevent** or diagnose a disease" (emphasis added - https://www.ema.europa.eu/en/glossary/medicinal-product).

1.2 International Regulatory Cooperation in Other Related Products

The scope of international regulatory harmonization and cooperation goes beyond medicines and vaccines and covers a broad array of related products, including personal protective equipment (PPE), medical devices (such as ventilators), in-vitro diagnostic tools, and even hand sanitizer. All of these products became centrally important during the COVID-19 pandemic, and as will be discussed in Section 3 below, the pandemic saw rapid changes to existing structures and procedures that saw NRAs embrace the (hitherto almost unknown or at least largely unarticulated) concepts of regulatory flexibility or agility (European Commission 2020). We discuss some of these actions in more detail below, **however, our focus remains predominantly on vaccines**.

1.3 Scope Limitations of the Current Research

The world has changed a lot due to the COVID-19 pandemic, and there are many ways in which public health systems and peoples' expectations of them have been forever and profoundly transformed. This is likewise true of regulatory harmonization and cooperation between NRAs, where the urgency that the pandemic and its economic and social aftermath gave rise to, required regulators across a broad range of fields and areas of government activity to find new ways of doing things, many of which were simply not possible without working with their counterparts in other countries. In this contribution, given the time and space constraints, we have chosen to focus primarily on international regulatory cooperation in the area of vaccines.

1.4 COVID-19 Pandemic a Time for Moving Fast and Breaking Things

As discussed in more detail in Sections 4 and 5 of this paper, the sheer scale of COVID-19 and the urgency felt by political leaders everywhere to gain control over the virus and navigate a return to socio-economic normality precipitated rapid and coordinated action to develop, test, authorize, mass-produce and distribute a vaccine on a hitherto unprecedented scale and at likewise unprecedented speed. There were many moving parts and different stakeholders in these various processes, all driving towards the same goal of inoculating as much of mankind against the virus as soon as possible.

One aspect of this urgent collaboration, which is the focus of this paper, was a hitherto unprecedented degree of cooperation between NRAs to authorize the use of as many new vaccines as possible, leading to what some observers have termed regulatory agility (Lim 2020, Bolislis et al 2021). This agility manifested itself in various forms, including expedited reviews and approvals, innovative approaches to streamline clinical trials, offering to conduct inspections of production facilities on a remote or virtual basis, flexible approaches to labelling, adoption of digital and online technologies to facilitate communication and interaction between regulators and other stakeholders (Bolislis at al 2021).

This paper concludes with a number of policy recommendations that seek to entrench the many gains and much of the forward momentum achieved during the pandemic on regulatory harmonization, so that the many lessons learned are not lost and so that the state of preparedness for future public health crises does not regress to pre COVID-19 levels, where they were obviously found wanting in many countries.

2. Regulation of Medicines

This section seeks to place the regulation of vaccines in its substantive context, namely within the broader framework of how medicines (of which vaccines are an important subcategory) are regulated. In doing so, it first discusses different aspects of how medicines are regulated in the modern economy, before turning to a discussion of the historical pedigree of medical regulation. It then discusses how various public health crisis have historically proven to be such important catalysts not only for new medical breakthroughs but also for regulation of the sector more generally and for increasing the responsiveness of regulators to public demands in particular. Next, this section discusses a number of processes and procedures that are at the heart of modern regulation of this sector before concluding with a discussion of both the technical complexity and governance challenges that pervade modern regulatory systems.

2.1 Different Aspects of Modern-Day Regulation

The distribution and consumption of medicines is regulated to one degree or another in almost all countries today. Regulation typically covers a number of areas, including but not limited to: 1) evaluation of data on the safety and efficacy of new drugs over the course of various trial stages (animal or human); 2) inspection and certification (licensing) of manufacturing facilities and distribution channels against contamination risks; 3) pre- or post-marketing monitoring of any reported adverse drug reactions (ADRs); and 4) ensuring that safety and efficacy claims made in relation to approved medicines in promotional and advertising materials are accurate (Britannica, 2021).[6] International regulatory cooperation (as discussed in more detail in subsequent sections of this paper), happens to varying degrees across all of these areas of activity but is arguably the most widespread in terms of (1) and (2). For these reasons, the lion's share of the analysis offered here likewise relates to these two regulatory functions and where international cooperation focuses on strengthening and improving them.

[6] Wang and Wertheimer (2021) add a number of other activities to this list, including development of regulatory policy and guidance, surveillance priorities and inspection programs, enforcement action clearance responsibility, and testing research.

2.2 Historical Pedigree

The approval of vaccines for public use, like the pre-market approval of medicines more generally, has a long historical pedigree going back to the manufacture of Mithridatium and Theriac (Griffin 2004), and today follows well-defined (albeit not harmonized) procedures in many countries. Comparative studies have shown that despite efforts over the last 30 years at regulatory harmonization, starting in Europe but also in other regions such as South East Asia, East Africa and the Americas (Regi 2017; Ndomondo-Sigonda et al 2021; and PAHO 2019), a high degree of variance remains between countries with regard to the form these procedures take, their duration, complexity, cost and the regulatory burden they impose more generally (Dukes 1986, Pezzola and Sweet 2016), not to mention the downstream impacts these variations exude on industry structures (Daemmrich 2009) and (more importantly) peoples' access to medicines (Roth et al 2018). These variations exist and persist despite the vast majority of these agencies essentially sharing the same fundamental goal, i.e., ensuring that new drugs are safe, efficacious and of high quality (NASEM 2020).

2.3 Progress Through Crisis Response

The process of establishing and improving the regulation of medicines, particularly in advanced industrialized countries, has often been in response to a related health crisis. For example, Ballentine (1981), as well as Thind and Kowey (2015), discuss the 1937 Elixir Sulfanilamide Incident, in which 105 people were fatally poisoned, resulting in a public outcry and demands for congressional action that culminated the following year in the Federal Food, Drug, and Cosmetic Act (FD&C Act).[7]

By the same token, Abed (2014) discusses the role the thalidomide tragedy of the 1960s played in the formation of new regulatory agencies throughout Europe. On a related note, Daemmrich (2009) goes into some detail on the impact that the AIDS crisis had on the U.S. FDA, particularly with respect to expedited approval of new and experimental medicines and treatments, and notes that a similar effect was largely absent from the European regulatory scene. As we will show later, the current (at the time of writing) COVID-19 pandemic has had a similarly dramatic impact on several important aspects of both the regulatory approval process at the national level as well as international regulatory cooperation in vaccines.

2.4 Processes and Procedures

The procedural modalities linked to gaining approval for a new drug differ from country to country, although there are a number of commonalities.[8] One of the most important

[7] 21 U.S.C. ch. 9 § 301 et seq.

8 Here we base our discussions primarily on the processes and procedures (and terminology) established and followed by the U.S. FDA.

and resource intensive steps, and in fact the first step that is specifically characterized by the involvement of the regulator, is the submission of an application by the sponsoring drug maker to investigate a new potential drug. In the U.S., this is called an Investigational New Drug (IND) application (Holbein, 2009, FDA 2021). In the EU, the national regulatory authorities in the different Member States are responsible for approving and overseeing clinical trials conducted on their own respective populations, albeit subject to standards and procedures adopted under EU law (EMA, 2019).

The IND application with the FDA's Center for Drug Evaluation and Research (CDER) seeks approval to proceed with human clinical trials and will generally consist of information the drug maker has compiled (in pre-clinical testing) on three essential test criteria, namely: 1) toxicity and pharmacology of the drug demonstrate that the drugs can be safely administered to human test subjects; 2) the ability to safely and consistently manufacture large batches of the drug to the same levels of quality; and 3) the proposed clinical protocols, including a demonstration of the competency of those conducting the trials and the informed consent documents of those on whom said trials will be performed (Thyne and Kowey, 2020). These three test criteria represent a high barrier for drug makers to clear before their products are approved to enter the market. Lesko and Woodcock (2004) posit that over 80 percent of new drug candidates that begin the IND application process fall by the wayside by failing to meet one or more of these criteria.

Human clinical trials take place in three phases. Phase I involves small numbers (between 20 and 80) of healthy volunteers, with the main objective of this phase being to identify both side effects and how the body metabolizes and excretes the drug (FDA, 2017). Phase II trials involve several hundred test subjects, all of which are afflicted with the underlying pathological condition the drug is intended to treat. Here the emphasis is on determining the drug's efficacy and in particular on determining a so-called therapeutic dosage window, meaning a dose at which "the efficacy and side effects are optimally balanced" (Thyne and Kowey, 2020). Finally, Phase III trials involve a significantly larger number of test subjects (from several hundred to several thousand) and involve "studying different populations and different dosages and using the drug in combination with other drugs" (FDA, 2017).

Only after Phase III trials have been successfully concluded does the sponsoring drug maker submit a New Drug Application (NDA) again to the FDA's CDER.[9] If the application document is complete (a factual determination the FDA has 60 days to make), the FDA begins its review, which includes the research findings resulting from the entirety of pre-clinical and clinical trials, information that will be provided to

[9] In the EU, the corresponding procedure is called a market authorisation application, see EMA, (2019).

consumers on the drug's labelling, and the facilities where the drug is manufactured (FDA, 2015).

2.5 Technical Complexity and Governance Challenges

Even a cursory browse through the available literature on the approval procedures for new medicines is enough to drive home the inherent technical complexity of this task This complexity comes in various forms, both in terms of the scientific and clinical knowledge required, but also the underlying governance structures that should ideally be in place in order to ensure that conflicts of interest and external pressures can be properly managed. Indeed, managing these governance challenges and mastering the scientific and clinical knowledge required are essential if the regulator is to meaningful pursue and perform its core public health objective, namely, to ensure that drugs are safe, efficacious and of high quality. Even in advanced industrialized countries, regulators find this challenging (Hawthorne, 2005 and Carpenter 2010). Clearly there is an important development dimension here given that many developing countries will lack either or both of these preconditions (Pezzola and Sweet, 2016). [10]

Yet another aspect that is important from a development perspective is that other factors beyond the above-mentioned asymmetries in expertise and governance also play an important role in constraining access to medicines for people in developing countries. The most important of these other factors is arguably that most of the largest as well as the most innovative drug makers are from advanced industrialized countries and prefer seeking marketing approval in either their home markets or other similarly endowed countries with regulatory structures and processes that they are already familiar with. The second other factor that favours the development and marketing of new drugs in advanced industrialized countries before they become available in the developing world is the fact that the former represent the most lucrative markets for generating returns for these drugs, simply because of the purchasing power of their resident populations and/or the fact that most residents enjoy some form of health insurance that covers the cost of these drugs (WHO, 2017). We discuss further development-related implications in subsequent sections of this paper, particularly when addressing the uneven distribution we have seen with regard to COVID-19

[10] The WHO in fact distinguished between four categories or "maturity levels" in terms of the technical and regulatory capacities of MRAs and the governance systems within which they operate, with level 1 being the least mature and levels 3 and 4 being the most mature. Using its Global Benchmarking Tool (GBT), the WHO has determined that with respect to the current status of regulatory systems for medicines and vaccines, some 100 countries are at Maturity Level 1, meaning only some elements of a regulatory system exist, with another 44 countries at Maturity Level 2, meaning that an evolving regulatory system is present that partially performs essential regulatory functions. The WTO furthermore notes that the 144 countries that together constitute Maturity Levels 1 and 2 can only ensure the quality of medicines on their markets if they rely on the regulatory systems of the 50 countries that have medical regulatory systems at Maturity Levels 3 and 4 (see WHO 2021b).

vaccines and the vastly different outcomes this had produced in developed and developing countries worldwide.

3. International Regulatory Cooperation in Medicines

This section discussed the evolution of regulatory cooperation between different NRAs and how this process functioned pre the COVID-19 pandemic (which is discussed in Part 4 of this paper). In doing so, it focuses first on the European experience, since this is where international regulatory cooperation between different NRAs was first successfully pioneered. It then turns to the factors that drive regulatory cooperation and the forms this takes today. Next, this section discusses a number of multilateral and regional approaches to regulatory cooperation, whereby a more in-depth appraisal of this phenomenon in the APAC region is the focus in Chapter 5 of this paper.

3.1 A Brief History

3.1.1 The European Experience

The forerunner of what we now understand as international regulatory cooperation in medicines can be found in the process of gradual harmonization that took place over the course of several decades of European integration. The initial foray into aligning different regulatory approaches was taken in 1965 with Council Directive 65/65/EEC.[11] This Directive sought to approximate procedures and standards in a number of important ways, including the principle that no medicine shall be placed on the market without prior approval (Art. 3), a set of minimum formal and substantive requirements for drug makers to meet before such approval can be granted (Art. 4), time-limits within which national regulators must review and decide upon applications for market approval from drug makers (120 days, with an additional 90 days possible under exceptional circumstances - Art. 7), the period for which such approvals are to be valid (5 years - Art. 10), enforcement actions related to post-market surveillance (Art. 11), and due process provisions incumbent upon Member-State NRAs with respect to their decision-making powers under the Directive (Art. 12). The 1965 Directive also sets out minimum requirements with regard to drug labelling (Art. 13 – 19). Interestingly for those who follow the various controversies over tensions between public health and trade liberalization, the 5th and 6th recitals of Directive 65/65/EEC appear to parse this question firmly in favor of the latter. Whereas the 5th Recital firmly acknowledges the

[11] Council Directive 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by Law, Regulation or Administrative Action relating to proprietary medicinal products (Official Journal 022, 09/02/1965 P. 0369 – 0373).

primary purpose of rules on the production and distribution of medicines is to safeguard public health, this is immediately caveated by the 6th Recital which states

> *Whereas, however, this objective must be attained by means which will not hinder the development of the pharmaceutical industry or trade in medicinal products within the Community.*

This seems somewhat shocking to any modern observer, since today - at least rhetorically - primacy is afforded to public health as a so-called higher-order priority, whereas the needs of industry and the imperatives of trade liberalization are often relegated to the status of subordinate interests. This likewise corresponds to the language of the GATT and GATS general exceptions, which – under certain conditions – afford governments the ability to set aside their WTO obligations if this is done in order to protect public health (WHO and WTO Secretariat 2004).

The process of regulatory harmonization took another big step forward in 1975, with the adoption of two new Council Directives; one on clinical testing of medicines prior to their marketing approval (Council Directive 75/318/EEC)[12] and another on facilitating the placing of medicines already authorized in one Member State. on the market of another, based on mutual recognition (Council Directive 75/319/EEC).[13] The 1975 Directives also provided for the establishment of the first supranational body in the regulation of medicines in the EU, namely the Committee for Proprietary Medicinal Products (CPMP), intended to "help EU Member States to adopt a common position with regard to decisions on issuing a marketing authorisation" (Abed 2014). The activities of the CPMP, discussed at some length by Sauer (2019) in his retelling of regulatory harmonization in Europe and beyond, provided a firm basis for national regulators and experts to work together and build the trust so essential to deeper and more formalized expressions of regulatory cooperation (Golberg 2020). More importantly, the development, by experts from governments, industry, and academia across Europe, of detailed technical guidelines covering many aspects of the approval process including quality, safety, and efficacy testing, as well as good manufacturing practices, set the stage for broader international cooperation and harmonization. As Sauer (2019), himself intimately involved with this process since the 1970s and the first Executive Director of the European Medicines Agency after it was established in 1995, notes

> *The availability of pharmaceutical legislation in all EU official languages had a deep impact on many continents. Scientists from all parts of the world had an*

[12] Council Directive 75/318/EEC of 20 May 1975 on the approximation of the laws of Member States relating to analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of proprietary medicinal products (OJ L 147, 9.6.1975, p. 1–12).
[13] Second Council Directive 75/319/EEC of 20 May 1975 on the approximation of provisions laid down by Law, Regulation or Administrative Action relating to proprietary medicinal products (OJ L 147, 9.6.1975, p. 13–22).

[sic!] easy access to a consistent body of scientific guidelines and procedural advice to applicant [sic!] (in English).

Today, the EU still operates according to a model that sees national regulatory bodies working with the European Medicines Agency on the basis of standards and procedures harmonized at the EU level, with the national agencies taking the lead in overseeing early clinical trials of new medicines - a role managed by the FDA in the U.S., with the latter working together with a local institutional review board (IRB).[14] The Member-State NRAs in the EU also play an important role in performing post-marketing surveillance (PMS) (Gough, 2005). The EMA plays a key role in what is today known as the centralized procedure. The institutional successor to the aforementioned CPMP is today the Committee for Medicinal Products for Human Use (CHMP) of the EMA, which is the equivalent to the FDA's CDER (discussed above). It is the CHMP which conducts the scientific evaluation of a marketing authorization application, and which issues its opinion on whether or not to approve a drug for marketing to the general public. This opinion is then forwarded to the European Commission, which issues a legally binding decision on the marketing authorization, that is valid not only for the 27 countries of the EU, but also Iceland, Liechtenstein, and Norway (although importantly not Switzerland, which as the home country of some of the world's largest pharmaceutical companies, has its own stringent regulatory authority, Swissmedic).

3.1.2 First Steps at International Regulatory Cooperation

1990 saw the launch of the International Conference for the Harmonisation of Pharmaceutical Requirements (ICH) between the EU, USA and Japan, with the goal being to "reduce unnecessary repetition of tests in humans and animals and duplication of costly stability and quality controls ... without compromising public health" (Sauer 2019). This initiative was launched at the behest of the European Commission and brought together actors comprising both government regulators and associations representing the research-based pharmaceutical industries in these regions (Lindström-Gommers and Mullin 2019). Over time, participation in biannual ICH meetings would grow to include experts and regulators from the, WHO, Canada, Switzerland and the global industry body, the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), which also provided the Conference with a secretariat. This mostly informal system of regular meetings and ongoing working groups was superseded by regional events and - in 2015 - the establishment of the International Council for Harmonisation of Technical

[14] An IRB is described by the FDA as an "appropriately constituted group that has been formally designated to review and monitor biomedical research involving human subjects" (FDA, 2018).

Requirements for Pharmaceuticals for Human Use (which retained the same acronym - ICH), with 16 members and 33 observers from all regions of the world.

Collaboration under the auspices of first the Conference and later the Council has produced significant outcomes including a dizzying array of guidelines under four distinctly classified areas, namely quality, safety, efficacy and multidisciplinary (i.e., cross-cutting). As the ICH itself notes, some of the harmonization outcomes achieved in the category of quality, include “defining relevant thresholds for impurities testing and a more flexible approach to pharmaceutical quality based on Good Manufacturing Practice (GMP) risk management”. By the same token, the ICH touts some of its achievements in the area of safety, including “a comprehensive set of safety Guidelines to uncover potential risks like carcinogenicity, genotoxicity and reprotoxicity” (ICH, 2021). A landmark set of outcomes, work on which began in the earliest days of cooperation, and which have culminated in widely accepted norms, include a common electronic format for applications – the Electronic Common Technical Document (eCTD) - and a common terminology – the Medical Dictionary for Regulatory Activities (MedDRA) (Sauer 2020, Lindström-Gommers and Mullin 2019).

3.2 Factors Driving Regulatory Cooperation

3.2.1 Asymmetries in Resources and Capabilities Between NRAs

As discussed above, the regulatory cooperation and ultimately harmonization that took place in the context of European integration was driven by the overarching imperative of creating a single market for the free circulation of all goods in Europe, including medicines. Today, a number of other imperatives are driving regulatory cooperation. One of these, also briefly alluded to above is the recognition that effective drug regulation is both complex and highly resource intensive. Only a handful of MRAs in the world arguably are capable of effectively managing the entire ambit of regulatory activities spanning pre-marketing approval to post-marketing surveillance (Olssen et al 2010; Pezzola and Sweet 2016). Even the most well-resourced and technically sophisticated struggle to fulfill their mandates to the complete satisfaction of all relevant stakeholders (drug companies, the public, doctors, patient advocacy groups, public-health NGOs, political leaders and others). Even the WHO recognizes this, and attributes this to “globalization of markets, the sophistication of health technologies, the rapid evolution of regulatory science and the increasing complexity of supply chains”, all of which conspire to make it unavoidable that NRAs “consider enhanced, innovative, more effective forms of collaboration to make the best use of the available resources and expertise, avoid duplication and concentrate their regulatory efforts and resources where they are most needed” (WHO, 2021b at p. 240).

3.2.2 Growing Complexity of Supply Chains

In their 2020 consensus study report on global trends in regulating medicine, NASEM come to the same conclusion, noting that "[drug] development, authorization, and regulatory supervision have become international endeavors, with most medicines now being global commodities" (preface). The report goes on to specify that "China is now the leading producer and exporter of APIs by volume, manufacturing more than 2,000 APIs" (p. 72), while India has also become a major production center, as its pharmaceutical sector "accounts for 71 percent of the market share of generic drugs and supplies more than 50 percent of the world's vaccines" (p. 73). The committee which authored the report concludes that "protecting and promoting public health in a time of globalization and unprecedented advances in technology and medicines—which are mirrored by the growing complexity of medicines and the supply chains for their manufacture and production—is the single greatest challenge facing medicines regulatory authorities today. (NASEM 2020, p. 28).

3.3 Forms of Regulatory Cooperation

Regulatory cooperation between different NRAs takes various forms, both formal and informal. In a technical briefing prepared in the context of capacity building efforts under its Global Benchmark Tool (discussed above, see footnote 6), the WHO describes the objectives of its Regulatory System Strengthening program, and in doing so defines one of these objectives as to promote regulatory cooperation, convergence and transparency through three activities, namely 1) networking, 2) work-sharing, and 3) reliance (Khadem 2019).[15] This section explores these three forms of regulatory cooperation in more detail.

3.3.1 Networking

Networking between NRAs has already been taking place for several decades thanks to the regular meetings organized under the auspices of the International Conference for the Harmonisation of Pharmaceutical Requirements. As already mentioned, this began first between regulators from the U.S., EU, and Japan, before expanding to include experts from other well-resourced regulatory bodies in countries such as Canada, Switzerland, Australia and New Zealand. It was finally opened up more broadly and became formalized as the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (discussed above).

Various other fora exist that allow regulators from different NRAs to meet informally albeit to discuss and share expertise on substantive areas of expertise, the most

[15] The other objective of this program, in fact the first, is – as the name *Regulatory System Strengthening* suggests – to "build regulatory capacity in Member States consistent with good regulatory practices".

important of which is of course the WHO itself, which organizes dozens of meetings every year, both in Geneva but also at the regional level. Other multilateral and regional organizations do the same, such as the WTO, the UN, the World Bank, the Asian Development Bank, APEC, ASEAN etc. (regional cooperation efforts are discussed in more detail in Section 3.4 below).

Networking activities between regulatory agencies might also include twinning of regulatory agencies, staff visits and exchanges (Margareth Ndomondo-Sigonda et al 2017; WHO 2021b). For example, the Croatian NRA HALMED[16], as part of its extensive and multi-year capacity building efforts in the context of the country's accession to the European Union, undertook a twinning program with its Spanish counterpart AEMPS.[17] This program lasted from December 2010 to June 2011 and involved 11 visits by 30 AEMS officials to conduct training seminars and workshops, as well as 2 study tours by HALMED staff to the Spanish official medical control laboratory (OMCL) network partner - see immediately below - (Tomić 2011).

3.3.2 Work-Sharing

A recent WHO technical report describes work-sharing as "[a] process by which NRAs of two or more jurisdictions share activities to accomplish a specific regulatory task" and goes on to note that "[t]he opportunities for work-sharing include joint assessment of applications for authorization of clinical trials or marketing authorizations, joint inspections for good practices, joint post marketing surveillance of the quality and safety of medical products, joint development of technical guidelines or regulatory standards and collaboration on information platforms and technology" (WHO 2021b). Work-sharing is thus an important mechanism for building the trust that is so essential if NRAs are to be able to practice reliance (discussed immediately below) to any meaningful degree NASEM 2020). One example of such a work-sharing arrangement is that of the Australia–Canada–Singapore–Switzerland United Kingdom ACCESS Consortium, formed in 2007, and which sees NRAs from these countries working together on initiatives such as the New Active Substance Work-Sharing Initiative (NASWSI) (TGA 2021a). The Consortium describes its goal as "to maximise international cooperation, reduce duplication, and increase each agency's capacity to ensure consumers have timely access to high quality, safe and effective therapeutic products" (TGA 2021b).

A distinct form of work-sharing is a joint activity, joint assessment or joint inspection. Here the goal is not to avoid duplication, so much as to encourage it under the mantra of "two sets of eyes see better than one". The WHO describes this sort of arrangement

[16] HALMED stands for Agency for Medicinal Products and Medical Devices of Croatia.
[17] AEMPS stands for Spanish Agency for Medicine and Health Products.

as “a form of work-sharing whereby a regulatory task is conducted by two or more NRAs in collaboration in order to share their assessments, benefit from each other’s expertise and discuss any shortcomings of the data evaluated” (WHO 2021b). In the case of a joint assessment, this may involve an application being submitted to two separate NRAs concurrently, allowing them to conduct their evaluations at the same time and share any findings and conclusions they reach. This also reduces the possibility that an important factor may be overlooked or underappreciated. A joint inspection by the same token would involve staff from two separate NRAs conducting an inspection of the same facilities, (either simultaneously or asynchronously), with each authority being tasked with different and discrete aspects and elements of the inspection in question (WHO 2021b).

3.3.3 Reliance

The most important instance of regulatory cooperation is reliance, which can manifest itself in various ways along a gradient of steadily increasing formality. The report by NASEM cited above refers to the range of different approaches and methods to facilitate reliance (and recognition discussed below) as “arrangements” and acknowledges that these can be more or less formalized in their conceptualization and operation. For example, the establishment of ad hoc committees, working parties or other dedicated working groups assembled to focus on a specific API or set of processes constitute less formalized expressions of reliance, whereas memoranda of understanding (MoUs), confidentiality agreements or mutual recognition agreements (MRAs) – the latter of which are particularly important in the area of medicines – are all more formalized instruments by means of which regulatory cooperation takes place that and which to share the considerable burdens that NRAs must bear.

Reliance can also be categorized as either horizontal or unidirectional.[18] The former takes place between NRAs that operate at roughly the same level of technical sophistication and resource-endowment, such as between those discussed above in the context of the ACCESS Consortium, or between the EMA and the FDA. Unidirectional reliance on the other hand involves less well-resourced NRAs, particularly those in developing countries, relying on the regulatory decisions or work products (assessment reports etc.) of better-resourced NRAs, particularly those in advanced industrialized countries.

3.3.4 Recognition

Recognition is a subgroup of reliance and has been termed “the ultimate form of reliance” (NASEM 2020). The WHO categorizes this form of cooperation as “a special

[18] These terms are borrowed from the 2020 report of the U.S. National Academies of Sciences, Engineering and Medicines cited above.

and more formalized approach to reliance" and goes on to articulate that this involves one NRA recognizing "the decisions of another regulatory authority, system or institution, obviating additional regulatory assessment to reach its own decision". (WHO 2021b, p. 245). NASEM, in its 2020 report, notes that the unwillingness of some NRAs to share completely unredacted decisions or assessment reports represents a serious constraint on the ability of dependent NRAs to rely on these works, and accordingly NASEM advocates for the sharing of unredacted documents (NASEM 2020, p 13).

3.3.5 Mutual Recognition

Mutual recognition has taken on overarching importance in the area of regulatory cooperation between NRAs and is a formal instrument by means of which two MRAs agree to recognize each other's decisions and/or work products. Mutual recognition is usually predicated on binding agreements either between the cooperating NRAs, or they take the form of binding international treaties negotiated at the level of governments. (WHO 2021b). The 2020 NASEM report lists 14 MRAs currently in force in the area of regulation of medicines, all of which are between NRAs that can be considered the "most mature" under the WHO nomenclature (Khadem Broojerdi et al 2020).[19] These MRAs typically concern issues or processes such as GMP inspections batch certifications product, packaging and labelling standards conformity assessment requirements GLP inspections and acceptance of industrial products (NASEM 2020).

There are a number of proposals to increase the impact of mutual recognition, including decoupling them from trade agreements (where they are usually negotiated) so that they may be bilaterally worked out between NRAs directly. This, it is argued, would allow these agreements to be concluded faster and without being held hostage to the other (unrelated) bargaining and concessions which typically characterise the horse-trading that makes the negotiations of trade agreements such a protracted matter. Another recommendation is to expand their substantive scope beyond the limited set of issues they currently cover (see immediately above).

3.4 Multilateral-Driven Cooperation by WHO

It is hard to overstate the importance of the WHO in terms of its contribution to regulatory cooperation between NRAs. This contribution has already discussed the WHO's efforts in Regulatory System Strengthening (RSS) though its Benchmarking Tool (WHO 2021b). Other ways in which the WHO supports regulatory strengthening and harmonization activities is by developing common standards for pharmaceutical processes and regulation, as well as supporting the regional cooperation mechanisms

[19] The 14 MRAs in question are all between NRAs in either Australia, Canada, the European Union, Israel, Japan, Iceland, Lichtenstein, New Zealand, Norway and the United States.

discussed immediately above. The WHO's Prequalification Program can result in accelerated marketing authorizations for medicines in as little as three months (ADB 2016). As discussed in Section 4 below, the WHO likewise took on a central role in the international regulatory cooperation that characterized the race to vaccinate humanity against the 2019 novel coronavirus.

3.5 International Coalition of Medicines Regulatory Authorities (ICMRA)

The ICMRA was established in 2012 in the face of growing recognition by the heads of a number of NRAs of the need for coordinated leadership to "address current and emerging human medicine regulatory and safety challenges globally, strategically and in an ongoing, transparent, authoritative and institutional manner" (ICMRA 2021). A number of the specific challenges this initiative seeks to address include the growing complexity in both "manufacturing and distribution supply chains for medicinal products" and in "medicinal products and their ingredients (e.g. new chemical entities and innovative drugs)" (ICMRA 2021). At the time of writing (May 2022), the ICRMA comprises some 24 member NRAs from countries as diverse as Australia, the EU, USA, Japan, South Korea, Mexico, India, Nigeria, South Africa and China (ICMRA 2021). In addition to its member NRAs, the ICRMA also has associate members from 13 countries at different maturity levels, and the WHO as a permanent observer. As discussed in Section 4 below), the ICMRA assumed a key function in the race to approve and distribute vaccines at the height of the COVID-19 pandemic.

3.6 Regional Cooperation Mechanisms

A number of regional initiatives have proven highly effective at promoting cooperation of one of the forms discussed in the previous section, and this is true across regions as diverse as East Africa, Southern Africa, the Americas, and the Asia-Pacific. To name just one example from Sub-Saharan Africa, the so-called ZAZIBONA process (involving NRAs from Zambia, Zimbabwe, Botswana and Namibia), which is a collaborative procedure for registration of medicines under the auspices of the Southern African Development Community (SADC), managed to shorten timelines for drug registration in the participating countries from years to months (Ndomondo-Sigonda et al 2021).

In the Americas, the Pan American Network for Drug Regulatory Harmonization has, among other achievements, successfully initiated "harmonization activities for small molecule i.e. nonbiological, less complex medicines" (ADB 2016), as well as drafting Guidelines on Good Regulatory Cooperation Practice that went on to be universally adopted by the WHO.

In the Asia-pacific region, a number of initiatives stand out, including the Pharmaceutical Products Working Group of ASEAN, which “has developed its own guidelines on technical requirements and what information marketing authorization applications should include” (ADB 2016). Another highly relevant initiative in region is the Asia-Pacific Economic Cooperation (APEC) Life Sciences Innovation Forum, which convenes a Regulatory Harmonization Steering Committee whose aim is to “promote a coordinated approach to medical product regulatory harmonization and capacity-building efforts within the APEC region” (ADB 2016). This paper discusses regulatory cooperation in the APAC region in more detail in Section 5.

4. Intergovernmental Cooperation and the COVID-19 Pandemic

4.1 Initial Responses from the G20

The pandemic saw a scramble among countries to acquire scarce resources in the initial demand and supply shocks that characterized the first weeks and months of the COVID-19 crisis (Tooze 2021, Bradley 2020; OECD 2020). This period was primarily one of competition and not cooperation, but this quickly changed. By the end of March 2020, barely two weeks after the WHO had declared the outbreak a pandemic, G20 leaders convened an extraordinary summit and had pledged a series of actions, including sharing timely and transparent information, exchanging epidemiological and clinical data, sharing materials necessary for research and development, expanding manufacturing capacity to meet the increasing needs for medical supplies and ensuring these are made widely available, at an affordable price, on an equitable basis (G20 2020a). This was accompanied by specific commitments to “close the financing gap in the WHO Strategic Preparedness and Response Plan” and “provide immediate resources to the WHO’s COVID-19 Solidarity Response Fund, the Coalition for Epidemic Preparedness and Innovation (CEPI) and Gavi, the Vaccine Alliance” (G20 2020a). One tally counted some 21 billion dollars in pledged financing to support “diagnostics, vaccines, therapeutics, and research and development” (Reuters 2020). This statement was followed by others from G20 leaders over the course of the year, culminating in the Declaration of G20 Health Ministers, adopted in Rome in early September (G20 2020b).

4.2 Multilateral Responses from Diverse Sectors

In April 2020, shortly after the G20 meeting discussed above, a broad coalition of different partners assembled under the joint leadership of the European Commission, France and the WHO, to establish the Access to COVID-19 Tools Accelerator (ACT),

which pooled the resources, capabilities and energies of “governments, global health organisations, manufacturers, scientists, private sector, civil society and philanthropy” (Berkley 2020). One of the most important outcomes of this effort was COVAX, a multilateral response involving governments, the private sector (vaccine manufacturers) and non-governmental organizations (NGOs) such as the GAVI vaccine alliance, and the Coalition for Epidemic Preparedness Innovations (CEPI). By early 2022, COVAX had shipped over 1 billion vaccine doses to 144 countries, with 191 countries participating in the initiative (the vaccine distribution effort is discussed in more detail below). Another important feature of COVAX which distinguishes it from purely national approaches is the diversity of its vaccine portfolio. As GAVI itself has articulated, “COVAX has the world’s largest and most diverse portfolio of COVID-19 vaccines, and as such represents the world’s best hope of bringing the acute phase of this pandemic to a swift end” (Berkley 2020).

4.3 The Race to Develop and Mass Produce a Vaccine

Much has been written about the unprecedented speed with which not just one, but several vaccines were successfully developed, approved and then mass-produced to counter COVID-19 (Tooze 2021). As one commentator notes, just six weeks after Chinese researchers published the genome of the virus, a U.S. biotechnology company was able to notify authorities of a new vaccine candidate for the purpose of conducting clinical trials, and as early as April 2 - and thus less than a month after the WHO had declared a pandemic - “America’s National Library of Medicine listed 282 potential drugs and vaccines against the new virus and were [*sic!*] already recruiting patients or proposing to do just that” (Norberg 2020).

Under normal conditions, vaccine development generally takes about 10 to 15 years (The College of Physicians of Philadelphia 2018). Up until the COVID-19 vaccine, the fastest vaccine that had been developed was that for the mumps, which took 4 years (Cohen 2020, Solis-Moreira 2021). Given the catastrophic impact COVID-19 had from the earliest days of the pandemic, both on countries’ public health systems but also their economies and the social fabric of cities and communities around the world, it was imperative that a vaccine be found as soon as humanly possible. The WHO coordinated an international response that pooled information, allowed researchers to agree on the most promising candidates, and subsequently scale up clinical trials across multiple countries (United Nations Department of Global Communications [DGC] 2020, Voysey et al 2020). With applications being reviewed for different vaccine candidate by stringent NRAs such as the UK’s Medicines & Healthcare products Regulatory Agency (MHRA) and the FDA, the first emergency use authorizations

started to be issued in December 2020.[20] The WHO issued an Emergency Use Listing (EUL) for the Pfizer/Biontech vaccine on 31 December 2020, thereby "[opening] the door for countries to expedite their own regulatory approval processes to import and administer the vaccine" (WHO 2020).

4.4 Making a Virtue out of Necessity through Regulatory Agility

The large amount of literature compiled since efforts to develop, test, approve and market a COVID-19 vaccine, documents the extraordinary and unprecedented degree to which NRAs chose to make a virtue of necessary and develop or expand upon regulatory agility to a degree never seen or even imagined before. For example Avorn and Kesselheim (2020) note that in June 2020, while announcing its expectation that any new vaccine "would reduce the occurrence or severity of disease in at least 50% of recipients" (and thus a success rate similar to that demanded of annual flu vaccines), the FDA also conceded that it might entertain "less conventional approaches", one of which would be to allow for "accelerated approval" of a vaccine candidate, based not on the results of actual stage 3 clinical trials, but rather on the basis of "antibody levels or another biochemical market" (Avorn and Kesselheim 2020, p. 1284). Ultimately the FDA authorized the Pfizer-BioNTech COVID-19 Vaccine on 11 December 2020 under an Emergency Use Authorization (EUA) on the basis of results from phase three trials involving 37,586 participants who were enrolled "in an ongoing randomized, placebo-controlled international study", with the majority of these participants being in the United States (FDA 2020).

Another example of regulatory agility that resulted from the pandemic and which was aimed at the expedited regulatory approval of vaccines as they were rapidly being developed, was the formation within COVAX (discussed above), of a Regulatory Advisory Group (RAG), co-led by the WHO and the Coalition for Epidemic Preparedness Innovations (CEPI), comprising representatives from 10 NRAs from different countries and regions to deliberate upon and provide feedback with respect to vaccine development by different manufacturers.[21] For example, in order for vaccine developers to obtain more coordinated feedback from NRAs, the RAG recommended that developers "simultaneously approach several agencies in parallel, e.g. four, including at least one stringent regulatory authority, in different geographic regions with the same data package and give permission to allow the agencies to exchange information and discuss a coordinated feedback" (WHO 2021d, p.2).

20 The UK MHRA granted temporary use approval for the Pfizer/Biontech vaccine on 2 December 2020. The U.S. FDA issued an Emergency Use Authorization (EUA) on 11 December 2020.

[21] The countries and regions from which representatives of 10 NRAs constituted the Regulator Action Groups were Argentina, Australia, Brazil, Canada, Europe (EMA and the European Directorate for the Quality of Medicines & HealthCare - EDMQ), Ghana, Japan, Singapore and USA.

Yet another example of innovative approaches under the mantra of regulatory agility and which alleviated the burden on vaccine developers was in the area of GMP inspections. Here regulators, in light of travel restrictions and other difficulties, initially offered that GMP inspections "could be facilitated by mutual recognition of GMP inspections done by a stringent regulatory authority" (ibid, p. 4), before a number of NRAs such as the EMA, the US FDA, Health Canada, HAS Singapore and TGA Australia developed additional processes including remote/virtual inspections (ibid).

Yet again among efforts to increase regulatory agility by increasing collaboration among regulatory and once more under COVAX, was the establishment of Support Work to Advance Teams (SWAT) comprising groups of experts dedicated to "resolving technical issues and challenges common across all COVID-19 vaccine development projects" (McGoldrik, Gastineau, Wilkinson et al 2022, p. 1217). For example a Manufacturing SWAT was established with representatives from regional and global industry associations to focus on a number of manufacturing challenges such as securing sufficient capacity for the initial production and then scaling of vaccine supplies, securing raw materials and other supply chain concerns, support for batch release testing (ibid).

These and numerous other examples show that as the scale of the pandemic took on proportions unprecedented in recent history, and both its health and economic effects became politically unbearable, regulators scrambled to pull out all the stops to rapidly test and approve new vaccines. However, it is also important to note that they did this while at the same time adhering to the highest standards of scientific rigor and medical safety. These standards had long been forming as part of regulatory collaboration initially between a small group of stringent NRAs, but which over time became broader and more inclusive and ultimately enjoyed the legitimacy afforded these efforts by their close association with organizations like the World Health Organization and multi-stakeholder initiatives like COVAX and CEPI.

5. Regulatory Cooperation and Vaccines in Asia-Pacific

In the Asia-Pacific region, a number of initiatives are worth mentioning with regard to regulatory cooperation to both mitigate the health and economic impacts of the pandemic, but also to promote regulatory agility in the approval and distribution of vaccines, each discussed in turn below under its own separate subheading. Compared to other regions, Asia-Pacific has performed relatively well in terms of both a source for developing new vaccines and successfully executing national vaccine rollouts.

At the level of distribution, the region played host to some of the countries that succeeded best in vaccinating a significant portion of their populations the fastest, such as Singapore, and - after initial stumbles - Australia.[22] Even some of the region's LDCs such as Cambodia succeeded in achieving remarkably high vaccination rates within a relatively short timeframe. But there are also more sobering statistics that attest to the varying degrees of success that have characterized governments' responses to COVID-19 across the region. Both public health systems that proved to be under-resourced, but also the administrative capacity to navigate recurring outbreaks as new variants of the virus emerged to ravage the region, all provided challenges to a number of governments.

5.1 Asian Development Bank-Led Initiatives

As a regional development bank with deep ties to and intricate knowledge of the Asia-Pacific region, as well as an established presence thanks to in-country offices, almost no organization was better placed than the ADB to identify and address the most urgent problems confronting economies as the pandemic unfolded across the region and this was true with regard to both the public health and economic impacts of the virus.

5.1.1 Asia Pacific Vaccine Access Facility (APVAX)

In December 2020 and thus just as the first emergency use approvals were starting to be issued in the U.S. and the UK (and later in the month by the WHO), the Asian Development Bank (ADB) proposed the Asia Pacific Vaccine Access Facility (APVAX) in response to the resource constraints faced by many developing country members (DMCs) of the regional development bank (ADB 2020). The initiative was essentially a USD 9 billion financing facility comprising two core components: one a rapid response element intended to provide quick access to diagnostic resources and vaccines; the second component comprised financing and support towards more long-term and systemic efforts to improve distribution, including transport, storage and administration,

[22] By December 2021, Singapore had inoculated […] of its population with 2 doses of either the […] or […] vaccine. In Australia, the corresponding figure was […], with the AstraZeneca, Pfizer-BioNTech and Moderna vaccines being favoured by the national vaccine rollout.

with this component also supporting institutional capacity building and post-market surveillance (ADB 2021a). As of September 2021, the ADB reported that it had "committed a total of $20.8 billion to the COVID-19 response including vaccination support in its developing member countries. Of this, assistance to the private sector totals $4.9 billion. Under APVAX, ADB has committed a total of $2.3 billion" (ADB 2021c).

5.1.2 Budgetary Support for Thailand

In addition to APVAX, the ADB was also providing support to individual DMCs under various country-specific programs. One example of this kind of support was the COVID-19 Active Response and Expenditure Support (CARES) Program, by virtue of which the ADB had agreed to extend a USD 1.5 billion loan to the Thai Government to support the latter's response to the pandemic, particularly the socio-economic impact it was having on the country's people (ADB 2022). These funds were used by the Thai authorities to support a domestic stimulus program and make cash payments to those most hard-hit by the economic impact the pandemic had, particularly on tourism and related services. (ADB, 2020).

5.2 ASEAN Initiatives

Efforts by ASEAN at closer regulatory cooperation in the area of medicines (and thus by extension vaccines) had long preceded the COVID-19 pandemic and had their roots in efforts to more closely integrate the different national economies to form a single regional market (Lätzel 2007). Below we discuss a number of these initiatives in more detail and show how, like in other regions, the pandemic and the urgency of overcoming the deep and multi-faceted disruptions it caused, drove new approaches to regulatory agility and promoted regulatory cooperation beyond anything that had been experienced previously.

5.2.1 ASEAN Pharmaceutical Product Working Group (PPWG)

The PPWG was the result of broader efforts to eliminate technical barriers to trade under processes that were part of ASEAN's 1992 FTA, particularly those of its Consultive Committee on Standards and Quality (ACCSQ) (Lätzel 2007). The PPWG was established in 1999 to support two objectives. The first was the removal of technical barriers to trade in pharmaceutical products. The second was facilitating access to these products in ASEAN "without compromising" their "safety, efficacy and quality".[23]

[23] Article 1 of the PPWG's Terms of Reference, available at: https://www.tisi.go.th/data/interstandard/pdf/asean/asean_ppwg_tor_2_6.pdf

Over the years, the PPWG has achieved some notable successes in areas such as harmonized requirements for the ASEAN Common Technical Dossier and the ASEAN Common Technical Requirements (both achieved in 2008), or a regional MRA on GMP (also in 2008) and for Bioequivalence Study Reports of Generic Medicinal Products (2018). However, the reality immediately prior to the COVID-19 pandemic was that "regulatory processes for obtaining marketing authorizations" were still "highly country-specific" and this "despite regional harmonization efforts" (Tongia 2018).

5.2.2 ASEAN Joint Assessment Coordination Group

The JACG was launched under the auspices of the WHO in 2017 as a mechanism for streamlining approvals for pharmaceuticals across participating ASEAN Member States. The way the scheme essentially works is that a single marketing authorization application is simultaneously filed with all participating ASEAN NRAs, who then work collaboratively to produce a joint assessment report (HSA 2016). Although the ultimate aim of the Joint Assessment procedure was to facilitate authorization procedures and thus expedite access to medicines that are tested and thus are deemed to be safe, of high quality and efficacious, this was also very much a capacity building exercise under the WHO's existing Regulatory Systems Strengthening RSS efforts. In order to qualify for the Joint Assessment procedure, drug candidates already had to have gained (at least tentative) approval by at least one SRA (generally the EMA or the U.S. FDA) or have been prequalified by WHO-PQP. Another qualifying criteria for admission to the ASEAN Joint Administrative procedure was that the drug candidate in question be aimed at treating a priority disease in the ASEAN region (HSA 2020).

5.2.3 ASEAN-OECD Good Regulatory Practices Network (GRPN)

The GRPN is an OECD-led[24] joint initiative that is co-chaired by New Zealand and Malaysia, and which brings together representatives from some 70 NRAs from both ASEAN and OECD Member Countries as well as representatives from regional and international organizations. The group first met in 2015 and has since met annually, with a focus first on good regulatory practice but more recently also on quality regulation and sound regulatory governance (OECD 2021a). This is essentially a platform for information sharing and exchanging experiences, although during the COVID-19 pandemic the initiative went into overdrive to provide as much support as possible to ASEAN NRAs. For example, by the end of 2021, the GRPN had met five time since the start of the pandemic "focusing on the changes to regulatory policy making associated with governments' responses to the pandemic and how better regulation reforms can support recovery" (OECD 2021b).

[24] This is to say that the initiative is managed by the OECD's Regulatory Policy Division.

5.2.4 ASEAN Member States Embrace Regulatory Agility

Although leaders and policymakers in ASEAN Member States recognized how much had been achieved over the years by the gradual and painstaking collaborative efforts of pharmaceutical regulators meeting and working at the ASEAN level in processes like the PPWG and JACG described above, it was likewise clear that these mechanisms and processes were not a viable option for the kind of regulatory agility required in the face of the looming public health disaster that COVID-19 spelled for countries in the region. As a result, Member States pursued their own solutions for procuring and authorizing different vaccines for their populations. In light of the very different approaches and outcomes that ASEAN represents in terms of both the pooling of national sovereignty and resources compared to the supranationalism that characterises the EU generally as well as the EU's approach to the vaccine rollout, at least one commentator has pointed out that the approach taken by leaders and regulatory bodies in ASEAN was arguably the correct one for the region (Lim 2021).

Indeed, the fact that each ASEAN Member State essentially opted for their own responses in terms of whether to close borders, the degree to which lockdowns and other social distancing measures were imposed and other emergency decisions taken to safeguard their own populations, is a testament to the extreme pressure governments were feeling in the early days of the pandemic. This was compounded by the fact that so little was initially known about the new virus (in terms of its nature and transmissibility) and that expectations at the outset were that a vaccine would take several years to develop. Add to this the fact that no region-wide emergency pandemic preparedness plan was in place, and the fragility of many AMS's public health systems in their capacity to deal with a national health emergency, and it is really no wonder that "urgent socio-political considerations [took] precedence over regional regulatory cooperation" (Lim 2021).

5.3 Asia Pacific Economic Cooperation (APEC)

APEC's response to the COVD-19 pandemic was a combination of ministerial summitry, joint political declarations and technical best-practices guidelines to support member governments manage different policy aspects of coping with and overcoming the various challenges the pandemic poses. These initiatives span a range of different areas, each with a combination of high-level statements or declarations by ministers or other political leaders, as well as more granular economic and policy analysis intended to guide decision makers grappling with difficult and urgent decisions (APEC 2021).

5.3.1 APEC Life Sciences Innovation Forum

The APEC Life Sciences Innovation Forum (LSIF) was established in 2002 while Mexico was hosting APEC. The LSIF is a multi-stakeholder grouping that brings together representatives from government, industry and academia, and its importance has grown over the years so that today it has become the leading platform for APEC in health and life sciences. Its mission is essentially threefold: (1) harmonization with international standards; (2) to promote technical cooperation with a view to building capacity; and (3) serving as a platform for public-private collaboration in the field of life sciences innovation (APEC LSIF, 2022).

In terms of its contribution to regulatory cooperation during the COVID-pandemic, it was under the auspices of the Forum's Regulatory Harmonization Steering Committee (RHSC) that much of this work was undertaken. Established in 2008 under the chairmanship of Health Canada, the RHSC had long been working towards regulatory convergence for approvals of medical products under a strategic framework, the target date for completion of which was – coincidentally enough – 2020 (ibid), with key performance indicators (KPIs) being adopted by the group in 2018 to measure convergence across four areas of best practices (Chong et al 2021).[25]

5.3.2 APEC Regulatory Responses to Support Vaccine Distribution

One such initiative, on Securing Access to COVID-19 Vaccines and other Medical Products, has for example culminated in a number of targeted policy documents including the Best Practice Guidelines for APEC Customs Administrations to facilitate the distribution of COVID-19 vaccines and related goods, as well as the APEC Supply Chain Security Toolkit for Medical Products. The first of these documents aims to "strengthen the predictability, visibility and reliability of economies' vaccine supply chains and also send a strong signal to the global community that APEC is committed to expediting the successful rollout of COVID-19 vaccines" (APEC 2021), while the Toolkit is aimed at helping policymakers grapple with "areas of vulnerability in the medical product supply chain and the lifecycle of medical products", particularly with respect to substandard and falsified medical products (APEC 2021). We discuss some of the recommendations and guidance provided in these documents in the final section of this paper.

[25] These were: (1) The removal of the Certificate of Pharmaceutical Product (CPP); (2) The use of the Good Manufacturing Practices (GMP) certificate issued by the Pharmaceutical Inspection Cooperation Scheme (PIC/S) network; (3) The management of multiple manufacturing sites under a single license from the regulatory authority; (4) The use of risk-based evaluation based on reliance practices (Chong et al 2021, p. 2).

5.4 UN Economic and Social Commission for Asia and the Pacific (ESCAP)

Technically part of the United Nations, ESCAP is one of several regional Commissions and like the UN more generally, ESCAP has also risen to the challenge to offer its support to the region in various ways. One such way is the development of what it calls a “framework to support the socio-economic response of Asia and the Pacific to the COVID-19 pandemic” (ESCAP, 2020). In this framework, ESCAP builds on three main areas of work where it already has the benefit of significant expertise and established policy engagement with its regional members and can thus leverage these strengths with the urgency the situation demands. The three areas of work in question are: (1) protecting people and enhancing resilience; (2) supporting economic recovery; and (3) restoring supply chains and supporting small and medium-sized enterprises (SMEs) (ESCAP 2020).

6. Outlook and Policy Recommendations

6.1 Urgency as Driver of Regulatory Agility

The COVID-19 pandemic, despite the massive toll it has taken both in the loss of human life but also the devastating impact it has wreaked on livelihoods in many nations, and especially poor countries, nevertheless proved a boon for the decades-long effort to increase regulatory agility in approving medicines for use and bringing them to market (Lim 2021). To be sure, the circumstances surrounding the pandemic were a so-called “once-in-a-hundred-year event” (Cruickshank and Shaban 2020)[26], and the urgency felt by governments in the face of the negative health impact, the socio-economic hardships, and the potential political instability these factors gave rise to, made discovering, approving, and delivering a vaccine one of the most complex and urgent imperatives governments have had to face so far this century. The implication is that this newfound regulatory agility was undoubtedly the result of intense political pressure.

Another important factor, no less related to the unique urgency of the situation, was – a certain degree of vaccine hesitancy notwithstanding - the relatively diminished risk-adversity of affected populations, particularly given the size of the unmet need when weighed against the obvious health and economic risks COVID-19 engendered. This confluence of factors meant that both political leaders and more importantly regulators understood and came to recognize that as a rule people were generally clamoring for

[26] Cruickshank and Shaban (2020) pointedly note that “[while] the speed and consequences of the COVID-19 pandemic may seem to have come out of nowhere, for those who work in infection prevention and control (IPC), it comes as no surprise or shock”.

a vaccine, both because it promised some degree of protection from many of the negative health impacts of COVID-19, but also because it was seen as the fastest way to end the lockdowns and secure a return to normal economic and social life. As such there was greater risk tolerance for one or more vaccines that were new and without the many years of extensive clinical trial data (Mak et al 2020).

In many countries in the APAC region, like in Africa, there was also a distinct lack of regulatory capacity for the independent review and verification of clinical trial data relating to new vaccine candidates by NRAs and certainly not within the timeframe required to mount an effective response to the unfolding crisis, with the only exceptions being the NRAs of Japan, Singapore and Australia. This crisis it should be remembered, proved more and more challenging to governments as the pandemic wore on, because of the emergence of new strains that were both more transmissible and – at least before the advent of the Omicron variant- similarly virulent such as the so-called UK super-strain, the South African Beta strain, and the Indian Delta variant. As such, NRAs were forced to make a virtue of necessity, and rely on the tried and trusted emergency authorization procedures of stringent regulatory authorities like the U.S. FDA, the EMA and the WHO itself (Soumyanarayanan et al 2021), with many if not all NRAs in the region choosing to follow the example set by one of these SRAs.

By the beginning of 2022, the focus had shifted from regulatory cooperation in the approval of vaccines for emergency use, to other efforts such as procuring sufficient quantities of the vaccine, the appropriate time to administer booster shots, the optimum combination of vaccines to improve the efficacy of booster shots against a constantly mutating virus, and improving the exchange of information as countries moved to the post-market surveillance stage and as the need arose to remain vigilant both for any new variants as well as any as yet undetected adverse drug reactions that could be statistically significant. There is also a desire to entrench to one degree or another, much of the progress made in regulatory agility during the crisis, particularly by drug companies and others pushing for greater access to medicines generally.

6.2 Some Tentative Lessons Learned

The COVID-19 pandemic represented a steep learning curve for political leaders across the world, who had to quickly learn to absorb and take decisions on advice from epidemiologists, virologist and other specialized medical experts, assisted by health policymakers. Some leaders proved more receptive to dealing with the technical complexities of the underlying phenomenon and in accepting the health advice given while others maintained or asserted varying degrees of adherence to politically expedient solutions or ideological positions. In the end, a number of factors including the soundness of the policy response, but also geographic, climatic, and demographic

realities served to influence how successful countries were initially at flattening the curve and then later at procuring and rolling out vaccines.

Despite the high degree of uncertainty as to the nature of the virus in the first weeks and months, those countries which moved quickly to implement proven and well-understood infection prevention and control (IPC) measures, such as closing or at least carefully monitoring borders, imposing strict restrictions on the movement of persons across and within borders, and implementing testing and tracing protocols, proved the most successful at staving off disaster or at least rapidly curtailing smaller outbreaks as they occurred. As the virus evolved and mutated becoming more transmissible with each new variant and as lockdown fatigue among affected populations made restrictions on economic activity increasingly costly politically, many of the measures that governments had taken in the first wave proved insufficient in successive waves, particularly in the face of the more transmissible Delta - and then later - Omicron variants. The COVID-19 pandemic will have instilled many governments with a better understanding of which restrictions impose the greatest cost economically and politically and how best to manage the cost-benefits calculus of restrictions and their potential benefit to the public health system versus their socio-economic impact on different elements of society.

Those countries which had pre-existing outbreak preparedness systems either in place or at the ready fared better than those without. In many instances, this was a function either of a country's previous exposure to similar outbreaks such as the 2003 SARS virus (China, Hong Kong, Singapore, and Vietnam) or other bureaucratically entrenched sensitivities to biosecurity threats (Australia and New Zealand). Interestingly, the 2019 Global Health Security Index published a report produced after a simulation exercise involving a mock global pandemic that sought to test the pandemic preparedness of some 195 countries. Both the United States and the United Kingdom ranked as the most prepared according to this index, a finding that was soon proven to be misplaced. However, one finding contained in the GHS Index that proved prescient was the following:

> *The GHS Index analysis finds no country is fully prepared for epidemics or pandemics. Collectively, international preparedness is weak. Many countries do not show evidence of the health security capacities and capabilities that are needed to prevent, detect, and respond to significant infectious disease outbreaks.* (Cameron et al 2019, at p. 9)

No doubt, after COVID-19, outbreak preparedness will be a policy priority for many governments throughout the world for years to come. Indeed, it was the high degree of pandemic preparedness that allowed China – after some initial but short-lived

missteps, to sequence the virus so quickly and communicate this information to the world. Likewise, it was Singapore's outbreak preparedness and the protocols put in place following SARS that allowed it quickly to mobilize and organize effective decision-making at the very highest level of political leadership and have a dedicated task force up and running within days of the first reports of the mysterious new virus detected in Wuhan (see Singapore case study).

Yet another lesson that has been learned is the importance of achieving universal vaccination across all countries. Of course, a lot of lip service was paid by developed and developing countries on the need to avoid vaccine nationalism and to ensure vaccine equity between rich and poor. But when supplies looked like they were becoming constrained as they did at several junctions, national governments in producing countries did what their domestic populations demanded, which was to prioritise the needs of their own citizens first. There was also a good deal of vaccine hoarding by developed countries over the course of 2021 (Nebahay and Mason 2021). However, the recurring emergence and spread of new and more transmissible variants, particularly from developing countries like South Africa (Beta and Omicron variants) and India (the Delta variant) drove home the need to vaccinate the entire world, and that doing so as soon as possible is in the self-interest of all countries, rich and poor, if the world is to finally be able to put the health risks, economic instability and disruption of daily life due to the COVID-19 crisis behind it.

6.3 Policy Recommendations to Improve Regulatory Agility

The policy recommendations provided below seek to support governments and public health authorities in improving the regulatory agility of NRAs to better execute their mandate to uphold the three pillars of modern medicines regulation in ensuring the quality, safety and efficacy, of medicines through their various activities, including in particular the "licensing, control and monitoring of the manufacture, import, export, distribution, promotion, and advertising of medicines; assessing the safety, efficacy, and quality of medicines; and inspection and surveillance along the entire supply chain". (Bell, 2016).

6.3.1 Maintain Publicly Available and Up-to-date Lists of Approved Medicines

This may not be necessary in countries with a well-regulated and adequately financed public health system, but in many countries transparency deficits as to what medicines have been approved for public sale is still lacking or may be insufficiently communicated. This can be due to a variety of factors, including lack of clear legislative frameworks or regulatory authority to publish such a list. In other cases, such a list may exist but may not be easily accessible to the public, nor is it maintained in a format that is amenable to regular updates that can be easily disseminated to the broader public.

To properly address this issue, public health authorities need to ask a number of question, including whether this is something the NRA already does in a comprehensive or partial manner and if this is not being done, why, i.e., is this due to a lack of legislative and regulatory authority, or resource constraints or both?

As part of efforts to improve transparency around public health, and as part of broader digital transformation initiatives, governments should delegate the authority and allocate the necessary resources to the NRA to establish and maintain such a list. As a starting point, the WHO Model Lists of Essential Medicines can be used for both guidance on what medicines to include in the published national list as well as for how to go about setting up such a list (i.e., what information to provide on and how to catalogue different medicines).

6.3.2 Mandate Time-Limits for NRAs to Adopt and Publish Regulatory Decisions

The long delays that can ensue in the course of seeking and obtaining regulatory approvals are a common complaint for the pharmaceutical industry, although in some cases this can be due to issues beyond the NRA's controls, such as the integrity of clinical trial data. In other cases, resource constraints at the NRA will be the key bottleneck, a problem that can admittedly only be fixed with the necessary political will, but is also contingent on outside technical assistance and support.

Here, the process of remedying systemic delays begins with asking the right kind of questions, such as how long does it currently take for the NRA to adopt and publish regulatory decisions in the context of approval procedures? Also, is the current time required in line with those required by NRAs in countries at similar levels of economic development? Also helpful in this regard is an answer to the question of whether the COVID-19 pandemic resulted in the adoption and publication of regulatory decisions at a more expedited rate that has generally been the case prior to the pandemic, and if so, what can the NRA do in future to permanently adopt some of the expedited decision-making that it resorted to in response to the urgent need to approve one or more COVID-19 vaccines? Once these questions have been asked, the next logical question is what additional resources or authorizations would the NRA require in order to adopt such expediencies on a permanent basis?

As alluded to above, achieving permanent efficiency gains in the work processes of regulatory bodies requires both the political will and the administrative capacity to do a post-mortem of how the NRA expedited approvals during the COVID-19 pandemic and which innovations could be permanently adopted in future without compromising the NRA's core mission.

To do this, governments should carry out a study of time limits for the adoption and publication of regulatory decisions prior to and during the COVID-19 pandemic, identifying which innovations the NRA adopted to expedite the approval of COVID-19 vaccines. In addition to this, governments seeking to institutionalize any innovative expediencies achieved in response to COVID-19 will need to legislate the adoption of those innovations that can be permanently adopted without compromising the NRA's core mission, setting binding time limits for NRAs to adopt and publish regulatory decisions. This also requires appropriating and allocating sufficient resources as are necessary to support the NRA in the implementation of these new requirements.

For the purposes of accountability and in order to benchmark any progress made, governments should also require that the NRA provide a semi-annual accounting of its success or failure in adhering to these new time-limits, with any failures being accompanied by reasons for their occurrence and internal recommendations for how such failures can be avoided in future.

6.3.3 Prescribe the Use of the WHO Collaborative Registration Process for Prequalified Products

This is particularly important in countries with NRAs that lack the capacity or resources to manage and interpret complex clinical trial data or that otherwise struggle to muster the resources required – particularly medical and pharmacological expertise – to oversee and complete lengthy and detailed approval procedures. In many countries, the main obstacles to participation are likely to be either of a political-economy nature (i.e., existing market participants are more satisfied with the status quo), related to government concerns over a real or perceived diminution in regulatory sovereignty that joining the procedure may entail, or be due to resource constraints. In other cases, where regulatory capacity is already deemed sufficiently robust, this may seem unnecessary.

Questions that are useful in clarifying the need to adopt this recommendation include is the NRA currently participating in the scheme?[27] If it is not participating, what are the main hurdles to participation? Finally, governments need to ask whether there would be considerable benefits to the main stakeholders of the country's public health sector (consumers, medical practitioners, hospitals, medical insurers) in joining the scheme?

In this context, it is recommend that governments initiate a study on the costs/benefits of participating in the scheme and identify what the relevant constraints are. If the government can demonstrate that the benefits outweigh the costs and can overcome

[27] We note that some APAC NRAs are already participating in this scheme, such as Bangladesh, Bhutan, Laos, Malaysia, Philippines and Thailand; see: https://extranet.who.int/pqweb/medicines/collaborative-registration-faster-registration.

any identified constraints, approach the WHO on joining the scheme, who is more than willing to offer countries advice on how to go about doing this.

6.3.4 Adopt Concrete Steps to Promote Cooperation between NRAs

As noted previously throughout this paper, in the modern world of complex and fragmented pharmaceutical supply chains, cooperation between different NRAs is becoming not just desirable but essential, something that the pandemic demonstrated all too visibly. The main challenges to doing this lie in garnering sufficient political will on the part of participating governments, but also identifying and allocating sufficient resources.

The questions governments need to be asking themselves in this regard is to what extent is cooperation between the country's NRA and more advanced NRAs already taking place either under regional cooperation arrangements or at the WHO? Also important to ascertain in this context is which NRAs in which countries would be the likeliest partners and would yield the best results in terms of different forms of cooperation over different time horizons?

Here it is recommended that the government first Identify which forms of regulatory cooperation already exist with which foreign NRAs either in the region or at similar levels of maturity. Next, the government should identify those weaknesses in the regulatory capacity of the home NRA that can best be addressed through greater cooperation with foreign NRAs and adopt an action plan to facilitate this happening. Following this, it is recommended that the government seeking to upgrade its own medical regulatory capacity approach the governments of the foreign NRAs with which greater cooperation is sought and agree upon the terms and conditions subject to which such cooperation shall take place (MOU, MRA, etc.). Finally, secure and allocate sufficient resources to the development and implementation of such regulatory cooperation initiatives, if necessary, by approaching relevant donor organizations.

6.3.5 Define and Implement a Dedicated Capacity Building Program for the NRA

The pathways for improving the capacity of country's public health regulatory authorities are by now quite well understood and the WHO among others has an established track record of doing just this in countries like Bangladesh, Rwanda, and Vietnam. This is first and foremost a resource issue, but also involves challenges of retaining any upgraded capacity over the medium to long term, which is a perennial problem for all capacity building efforts

These efforts begin by asking what is the most cost-effective and impactful way in which capacity can be built in the short to medium term? It is also helpful to clarify

whether this would require large infusions of new resources and qualified staff and if so, how can such resources be secured (public budget and private sector contributions)? Also important from a human resource development perspective is the question of whether short-term improvements to resourcing and staffing are sustainable over time to avoid “leakage” of any upgraded human capacity to the private sector?

In terms of recommended measures to achieve this goal these include identifying which weaknesses in capacity are the most amenable to improvement over the short, medium and long terms. As well as identifying which avenues for capacity building are likely to be the most impactful and cost-effective (inhouse training, staff placements in foreign NRAs, secondments of staff from foreign NRAs, etc.). Governments are also advised to identify which foreign NRAs and other institutions can support them in its efforts to upgrade the capacity of their own NRA, through institutional twinning programs and similar efforts. Finally, it will be necessary to seek the help of capacity building experts in the field of regulatory approval of medicines at organizations like the WHO or stringent NRAs to support the government in drawing up and implementing its capacity building program.

7. Concluding Remarks

It was thanks to the extensive and deep-rooted ways in which the world has grown intricately interconnected that the novel b-coronavirus SARS-CoV-2 was able to spread so rapidly and infect millions of people in virtually every country of the world in such a short period of time. But it was also thanks to a wide range of formal and informal cooperation arrangements and linkages that scientists, public health officials, regulators, and political leaders from all over the world were able to unite behind the common cause of defeating the virus and restoring the world and the global economy to some semblance of normality.

This paper has focused primarily on the way governments successfully cooperated to expedite the approval and rollout of an initial set of vaccines developed in countries such as the United States, the United Kingdom, China and India. This was without doubt the fastest example in human history of such an effort and has proven yet again the resourcefulness and doggedness of the human spirit and what mankind is capable of when it unites its resources to achieve an identified goal.

However, the level at which governments cooperated during the pandemic went far beyond the narrow objective of developing and distributing vaccines. Governments

worked together across a range of different regulatory areas to exchange information and share experiences on what measures were proving the most effective across a range of challenging policy problems both related to public health but also the equally important goal of protecting the vulnerable from the many socio-economic deprivations that social-distancing and other IPC measures gave rise to.

As the fight against the pandemic continues, albeit with an increasingly broad and sophisticated range of medical responses and policy tools, governments of all countries would be well advised to catalog and internalize the many lessons learned over the last two years, to better prepare themselves, their populations and their economies against future tests and crisis

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Policies and Guidelines

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2. WHO, 2021; *Good reliance practices in the regulation of medical products: high level principles and considerations*, Annex 10 to the "WHO Expert Committee on Specifications for Pharmaceutical Preparations, Fifty-fifth report"; pp. 237 – 264; available at: https://apps.who.int/iris/bitstream/handle/10665/340323/9789240020900-eng.pdf
3. WHO, 2021; COVID 19 Vaccines: Safety Surveillance Manual | Regulatory Reliance and Work-Sharing 2nd Edition, available at: https://www.who.int/publications/i/item/9789240032781

4. European Medicines Agency (EMA), 2019, *From laboratory to patient: the journey of a medicine assessed by EMA*; available at: https://www.ema.europa.eu/en/documents/other/laboratory-patient-journey-centrally-authorised-medicine_en.pdf
5. US Food and Drug Agency (FDA), *Guidance Document: Emergency Use Authorization for Vaccines to Prevent COVID-19*, available at: https://www.fda.gov/media/142749/download

Websites of Organizations Promoting Regulatory Cooperation

World Health Organization

COVID-19 vaccines technical documents:
https://www.who.int/groups/strategic-advisory-group-of-experts-on-immunization/covid-19-materials

Capacity building and training materials:

https://www.who.int/activities/capacity-building-and-training-materials

COVAX:

https://www.who.int/initiatives/act-accelerator/covax

South-East Asia Regulatory Network (SEARN:

https://www.who.int/southeastasia/activities/south-east-asia-regulatory-network-(searn)

Organization for Economic Cooperation and Development

Regulatory Policy and the COVID-19 Crisis
https://www.oecd.org/regreform/regulatory-policy/reg-covid-19-activities.htm

Asia Pacific Economic Cooperation

Life Sciences Innovation Forum Regulatory Harmonization Steering Committee
https://www.apec.org/rhsc

International Coalition of Medicines Regulatory Authorities (ICMRA)
COVID-19
https://www.icmra.info/drupal/en/covid-19

Annex I
Future Preparedness Regulatory and Policy Benchmarking Tool

Issue 1 Maintain Publicly Available and Up-to-date Lists of Approved Medicines

Guiding Question

1. Is it clear which domestic institution has the authority to do this, or put another way, has the NRA been explicitly vested with this authority?
2. Is this something the NRA already does in part (for newly approved medicines) or in full (for all medicines including those long on the market)?
3. If this is not done, what technical or resource constraints exist to establishing such a register?

Potential Challenges

In many developing countries a **lack of clear legislative or regulatory authority** to provide this and **severe resource constraints** may hinder the establishment and effective publication of such a list. Moreover, such a list must be published in such a way that is both easily accessible to the public and can be easily updated by the authorities, i.e., **in digital and online format**, which again raises questions of **resources and skills** to establish and maintain such a list.

Recommended Measures

1. As part of efforts to improve transparency around public health, and as part of broader digital transformation initiatives, governments should delegate the authority and allocate the necessary resources to the NRA to establish and maintain such a list.
2. As a starting point, the WHO Model Lists of Essential Medicines can be used for both guidance on what medicines to include in the published national list as well as for how to go about setting up such a list (i.e., what information to provide on and how to catalogue different medicines).

Issue 2 Mandate Time-Limits for NRAs to Adopt and Publish Regulatory Decisions

Guiding Question

1. How long does it currently take for the NRA to adopt and publish regulatory decisions in the context of approval procedures?
2. Is this in line with average timeframes for NRAs in countries at similar levels of economic development?
3. Did the COVID-19 pandemic result in the adoption and publication of regulatory decisions at a more expedited rate that has generally been the case prior to the pandemic?

4. What can the NRA do in future to permanently adopt some of the expedited decision-making that it resorted to in response to the COVID-19 pandemic?
5. What additional resources or authorizations would the NRA require in order to adopt such expediencies?

Potential Challenges

For this particular recommendation, there must be both the **political will and the administrative capacity** to do a post-mortem of how the NRA expedited approvals during the COVID-19 pandemic and which innovations could be permanently adopted in future without compromising the NRA's core mission.

Recommended Measures

1. Carry out a study of time limits for the adoption and publication of regulatory decisions prior to and during the COVID-19 pandemic, identifying which innovations the NRA adopted to expedite the approval of COVID-19 vaccines.
2. Legislate the adoption of such innovations as can be permanently adopted without compromising the NRA's core mission, setting binding time limits for NRAs to adopt and publish regulatory decisions.
3. Allocate such resources as are necessary to support the NRA in the implementation of these new requirements.
4. Require the NRA to provide a semi-annual accounting of its success or failure in adhering to these new time-limits, with any failures being accompanied by reasons for their occurrence and internal recommendations for how such failures can be avoided in future.

Issue 3 Prescribe the Use of the WHO Collaborative Registration Process for Prequalified Products

Guiding Question

1. Is the NRA currently participating in the scheme?[28]
2. If it is not participating, what are the main hurdles to participation?
3. Would there be considerable benefits to the main stakeholders of the country's public health sector (consumers, medical practitioners, hospitals, medical insurers) to joining the scheme?

Potential Challenges

The main obstacles to participation are likely to be either of a **political-economy nature** (i.e., existing market participants are more satisfied with the status quo), related to government concerns over a real or perceived **diminution in regulatory sovereignty** that joining the procedure may entail, or be due to **resource**

[28] We note that some APAC NRAs are already participating in this scheme, such as Bangladesh, Bhutan, Laos, Malaysia, Philippines and Thailand; see: https://extranet.who.int/pqweb/medicines/collaborative-registration-faster-registration.

constraints. In other cases, where regulatory capacity is already deemed sufficiently robust, this may seem unnecessary.

Recommended Measures (for those countries not participating in the WHO scheme)

1. Initiate a study on the costs/benefits of participating in the scheme and identify what the relevant constraints are.
2. If the government can demonstrate that the benefits outweigh the costs and can overcome any identified constraints, approach the WHO on joining the scheme.

Issue 4 Adopt Concrete Steps to Promote Cooperation between NRAs

Guiding Question

1. To what extent is cooperation between the country's NRA and more advanced NRAs already taking place either under regional cooperation arrangements or at the WHO?
2. Which NRAs in which countries would be the likeliest partners and would yield the best results in terms of different forms of cooperation over different time horizons?

Potential Challenges

This is primarily a matter of both **political will and sufficient resources**, with the primary constraint being the latter, particularly since the pandemic has markedly changed the political calculus as to the need to have robust regulatory capacity on hand.

Recommended Measures

1. Identify which forms of regulatory cooperation already exist with which foreign NRAs.
2. Identify those weaknesses in the regulatory capacity of the home NRA that can best be addressed through greater cooperation with foreign NRAs and adopt an action plan to facilitate this happening.
3. Approach the governments of the foreign NRAs with which greater cooperation is sought and agree upon the terms and conditions subject to which such cooperation shall take place (MOU, MRA, etc.).
4. Allocate sufficient resources to the development and implementation of such regulatory cooperation initiatives.

Issue 5 Define and Implement a Dedicated Capacity Building Program for the NRA

Guiding Question

1. What is the most cost-effective and impactful way in which capacity can be built in the short to medium term?
2. Does this require large infusions of new resources and qualified staff? If so, how can such resources be secured (public budget and private sector contributions).
3. Are short-term improvements to resourcing and staffing sustainable overtime to avoid “leakage” of any upgraded human capacity to the private sector?

Potential Challenges

This is first and foremost a **resource issue**, but also involves challenges of retaining any upgraded capacity over the medium to long term, which is a perennial problem for all capacity building efforts.

Recommended Measures

1. Identify which weaknesses in capacity are the most amenable to improvement over the short, medium and long terms.
2. Identify which avenues for capacity building are likely to be the most impactful and cost-effective (inhouse training, staff placements in foreign NRAs, secondments of staff from foreign NRAs, etc.).
3. Identify which foreign NRAs and other institutions can support the government in its efforts to upgrade the capacity of its own NRA, through institutional twinning programs and similar efforts.
4. If necessary, seek the help of capacity building experts in the field of regulatory approval of medicines at organizations like the WHO or stringent NRAs to support the government in drawing up and implementing its capacity building program.

Annex II
Country Case Studies

1. India

The NRA responsible for approval of COVID-19 vaccines in India is the Central Drugs Standard Control Organisation (CDSCO), under the oversight of the Directorate General for Health Services of the Ministry of Health and Family Welfare. The CDSCO is led by the Drugs Controller General of India (DCGI) – currently Dr. V. G. Somani – an official appointed by the central government. The DCGI is advised by the Drug Technical Advisory Board and the Drug Consultative Committee.

Through a sprawling organizations structure that includes offices and laboratories throughout the county and in major ports, the CDSCO approves new drugs but also performs a range of other regulatory functions. These include import registration and licensing, the licensing of inter alia, blood banks, vaccines and some medical devices and diagnostic agents, as well as representing India in WHO GMP schemes. It is also the CDSCO that approves testing protocols, carries out its own testing, publishes the Indian Pharmacopeia, and takes the lead on post-market surveillance for adverse drug reactions. Interestingly, it is not the CDSCO which is responsible for pricing or even drug policy decisions, but rather the Ministry of Chemicals and Fertilizers by virtue of the National Pharmaceutical Pricing Authority (NPPA), which also maintains data on production, exports and imports, in addition to enforcing and monitoring the availability of medicines on the domestic market.

New drugs are only approved for marketing in India by the DCGI if they demonstrate that they are safe, effective and comply with Schedule Y of the Drug and Cosmetics Rules (1945) of the Drug and Cosmetics Act (1945), which sets out detailed guidelines and requirements for clinical trials. In 2006, a two-track system was introduced to expedite new drug approvals. For drugs which had already been approved by a stringent NRA (so-called “Category A” drugs), a fast-track approval procedure applies whereby drugs are approved for marketing in India within 2 to 4 weeks. For other (“Category B”) drugs, the deeper scrutiny required resulted in approval times of 12 weeks, once a complete application is submitted to the DCGI.

In 2017, an in-depth review (benchmarking) by the WHO of CDSCO found that the NRA had attained sufficient regulatory capacity to qualify it as a “functional” drug regulator, one classification below the maturity level required for an NRA to be considered a stringent regulator, and a distinction that only some 30 percent of NRAs in the world have earned. This positive assessment was critical for the country’s drug and vaccine industry, since it is a pre-requisite for WHO prequalification of vaccines.

For vaccines, the National Technical Advisory Group on Immunisation in India (NTAGI) was established in 2001 under the Department of Family Welfare within the Ministry of Health and Family Welfare, as part of broader efforts under the Universal Immunisation Program (UIP). A special working group on COVID-19 vaccines was established under

NTAGI and first met in August 2020. The input of NTAGI in the approval process is only of an advisory nature, and the advice emanating from NTAGI has deviated at times from the decisions taken on approvals of COVD-19 vaccines by the CDSCO, for example in August 2021, when the NRA approved ZyCoV-D for use in both adults and adolescents.

India approved its first two vaccines on January 3rd, specifically a domestically produced version of the UK's AstraZeneca vaccine, and the completely indigenous Covaxin, developed by Bharat Biotech. Approving the Indian vaccine proved controversial, given that at the time, its developer was still in the process of recruiting candidates for its Phase III trials. Over the course of the vaccine rollout, as additional vaccines have been approved, there has been some criticism of the CDSCO as some have questioned its ability to stand up to political pressure.

From the outset, India's efforts to develop and mass-produce vaccines was an effort steeped in international cooperation, not least because India's pharmaceutical industry had undergone rapid transformation over the two preceding decades to position the country as the foremost vaccine supplier to the world. As early as March 2021, the majority of India's vaccine manufacturers had signed exclusive licensing agreements with foreign partners for developing and manufacturing various COVID-19 vaccines, including with Oxford University and AstraZeneca for their vaccine, which was mass-produced in India and exported under the name Covishield, and the Russian-developed vaccine Sputnik V (approved by the DGCI in April 2021).

India's vaccine diplomacy efforts saw the country take the lead in exporting vaccines to countries as far and wide as Afghanistan, Bahrain, Bangladesh, Bhutan, Fiji, Guatemala, Kenya, Maldives, Mauritius, Mongolia, Mozambique, Myanmar, Nepal, Nicaragua, Oman, Paraguay, Sri Lanka, and Uganda. India was also a major supplier to COVAX, although the country temporarily suspended exports in March 2021 at the height of the Delta variant wave that swept the country in the end of 2020 and the beginning of 2021.

Sources: CDSCO website, Imran et al 2013, Pulla 2022, John 2010, Ministry of Health and Family Welfare 2017.

2. China

The NRA responsible for approval of COVID-19 vaccines in China is the National Medical Products Administration (NMPA), which was established in its current form in 2013 through a restructuring of various different regulatory agencies. In 2018, it took on its current name and was merged into the newly created State Administration for Market Regulation, a kind of super-ministry responsible for the regulation of market competition, monopolies, intellectual property, and drug safety, directly under the State Council of the People's Republic of China.

The NMPA's powers are wide-ranging and include drafting and implementing policy, legislation and regulation on food, drugs (including traditional Chinese medicines), medical devices and cosmetics. The NMPA also publishes the national pharmacopeia and is responsible for the registration (approval) and post-marking surveillance of drugs and medical devices.

According to a 2018 New York Times' report, in the first decade and a half of the new millennium, just over 100 new drugs were approved in China, which is about one-third the number that had been approved in developed countries, with approvals typically taking seven to eight years. However, this finding is contradicted by academic research undertaken by Dali Yang, who notes that in 2006 alone, the Chinese food and drug regulator approved 1803 new drugs, although some of these approvals had to be withdrawn subsequently for lack of regulatory stringency.

China's regulatory framework for medicines was assessed by the WHO under the organization's Benchmarking Toolkit in 2011 and 2014, after which, like India in 2017 (discussed above) it was recognized as a functional regulatory agency, thereby laying the foundation for WHO prequalification of Chinese vaccines.

After early stumbles surrounding how to deal with the initial outbreak in Wuhan, the central government leadership in Beijing moved quickly once the scale of the threat posed by COVID-19 became apparent. In responding to the new virus in the early months of 2020, the Chinese authorities approved large funding allocations for research and development, as well as pooling resources from various research institutions to focus on several areas, including new medicines and vaccines, of which potential candidates were identified across various categories, including inactivated vaccines, recombinant protein vaccines, live attenuated influenza vaccines, adenovirus vaccines, and nucleic acid-based vaccines. For its part, the NMPA wasted no time in reviewing applications for the approval of emergency medical treatments.

As a result of these efforts, by both authorities and the community of epidemiology researchers, China was able to identify and genetically map the novel coronavirus by 9 January 2020. By the end of the same month, the NMPA had approved four diagnostic kits for the virus, and by the end of May 2020, it had authorized 19 applications for clinical trials for medicines and vaccines to both prevent infection and treat infected patients.

By June 2020 (although some reports put this date as August 2020), an emergency use authorization had been issued by the NMPA for Sinovac's vaccine (also known as CoronaVac), making China one of the first countries to approve a COVID-19 vaccine candidate.

By its very nature, the Chinese efforts to develop and test different vaccine candidates relied on a high degree on international regulatory cooperation, since China's initial success in combatting the virus meant there were simply not enough patients for domestic phase III trials to be conducted within China. Instead, these trials were conducted in countries were the virus was both rampant and governments were eager to get their hands on any vaccine that they could obtain. These two preconditions prevailed in a number of large and populous countries, including Indonesia, Turkey and Brazil. Indeed, it was thanks to results from phase III trials conducted in these three countries that in February 2021, the NMPA approved a second Chinese vaccine (Sinovac) for general public use.

China also engaged in a huge vaccine diplomacy effort, sending mostly commercial exports of vaccines to countries in South-East Asia, Africa and Latin America (where it became the main supplier), as well as to Hungary, the only EU country that included Chinese vaccines in its domestic vaccination campaign.

By June 2021, the NMPA had granted conditional market or emergency use authorization to a total of seven domestically produced vaccines, two of which had also been listed by the WHO for emergency use.

Sources: Wee 2018, Yang 2009, Zhang et al 2021, Nolte 2022.

3. Singapore

The NRA responsible for approving COVID-19 vaccines and treatments in Singapore is the Health Sciences Authority (HSA), a statutory board under the Ministry of Health of the Government of Singapore. The HSA is a stringent regulator, that in February 2022 was assessed using the WHO Global Benchmarking Tool and was subsequently hailed as the world's first to achieve the highest maturity level in WHO classification (ML4) of regulatory authorities for medical products.

The HSA, which since 2019 is no longer responsible for food safety, has three functions under the governing legislation currently in force (the Health Products Act 2007), being the national regulator for health products, securing the national blood supply, and providing expertise in represents the national expertise in forensic medicine, forensic science, and analytical chemistry testing capacities. It is in executing this first function that the HSA evaluates product approval applications, oversees and assesses clinical drug trials, as well as auditing good manufacturing practices and conducting post-market surveillance of health products marketed in Singapore.

Through various memoranda of understanding, Singapore has formalized close working relationships with NRAs in other countries, including other stringent regulators such as the US FDA, Health Canada, Swissmedic, the Australian Therapeutic Goods Administration and with less mature NRAs such as the China Food and Drug Administration. The HSA also cooperates extensively with its counterparts in ASEAN member states thanks to long ongoing regulatory cooperation efforts in ASEAN, as discussed in the text of this paper (Section 5.2).

Particularly through its involvement in the ACCESS Consortium, comprising stringent NRAs from Australia, Canada, Singapore, Switzerland and the United Kingdom, Singapore's HSA worked on the articulation and dissemination of technical guidance on a range of issues, including the regulatory evidence requirements for COVID-19 vaccine approvals and considerations for post-market pharmacovigilance and later on COVID-19 medicines.

Singapore was the first country in Asia to approve the Pfizer-BioNTech's coronavirus vaccine for emergency use (known in Singapore as interim authorization) on 14 December 2020, just 3 days after the USFDA had done the same. The Singaporean government had been at the forefront of efforts to support promising vaccine candidates and secure vaccine supplies, investing heavily to sign advanced purchase agreements and make advance down payments to candidates in both the United States and China, including Pfizer BioNTech, Moderna and CoronaVac.

In August 2021, the Singaporean Ministry of Health announced that it would recognize all COVID-19 vaccines accepted on the WHO Emergency Use Listing (EUL) and by extension would confer fully vaccinated status to anyone who could demonstrate having been inoculated with a WHO-approved vaccine

It was Singaporean Prime Minister Lee Hsien Loong who is generally credited with coining the phrase “vaccine multilateralism” at the Global Vaccine Summit which took place in June 2020, offering whatever support the small nation state could provide in shaping the conversation around ensuring equitable access to COVID-19 vaccines. Singapore was also an early supporter of the COVAX Facility, and launched – together with Switzerland - the informal grouping known as the Friends of COVAX Facility (FOF) to catalyse discussions about the COVAX Facility and generate a significant body of support among self-financing countries to support efforts at achieving vaccine equity.

Given its overriding economic dependence on international travel and trade, Singapore consistently took the lead in efforts to restore normality, from being the first country to be fully vaccinated in August 2021, to opening its border with Malaysia barely a month later after each country agreed to mutually recognize each other vaccine certificates, to being one of the first countries to officially abandon a zero covid strategy in favour of one entitled “living with covid”.

Sources: HSA 2020, Bhatia 2020, Wikipedia 2022,

4. Cambodia

The national medical regulatory authority in Cambodia is the Department of Drugs and Food (DDF) under the Ministry of Health (MOH), established by virtue of the 1996 Law on the Management of Pharmaceuticals. In its capacity as NRA, the DDF regulates the market for a range of products and devices, including pharmaceuticals, traditional medicines, health supplements, food, medical devices, and cosmetics, with the power to approve or rejection applications for marketing authorization, and conduct post marketing surveillance and enforcement.

Although clinical trials are possible in Cambodia in theory, with the National Ethics Committee (NEC) of the National Institute of Public Health under the MOH having statutory authority to govern and regulate such trials, in practice, the NEC has never authorized any request to conduct clinical trials beyond basic questionnaire-based studies that do not involve the introduction of new or novel pharmaceuticals or medical treatments.

Given its status as an ASEAN Member State, Cambodia has enacted the ASEAN Common Technical Requirements (ACTR) and ASEAN Common Technical Dossier (ACTD), which together essentially outline the procedures and protocols subject to which pharmaceutical products must be manufactured, registered and maintained in the regional group.

A Chinese media report dated February 4, 2021 announced the recent emergency use approval, by the Cambodian health authorities, of the Sinopharm vaccine, of which a significant number of doses would ultimately be provided to Cambodia as part of its highly successful national vaccination campaign. This was followed, on 22 February,

by emergency use approval of the AstraZeneca vaccine by the Cambodian health authorities, approximately a week after it had been listed by the WHO for emergency use, with the first 300,000 doses of the UK-developed vaccine being delivered on 2 March 2021.

An October 2021 report lists some 20 vaccines all approved for emergency use in Cambodia, including the Russian Sputnik vaccine, the US Pfizer and Moderna vaccines, France's Sanofi vaccine and Cuba's Soberana vaccines, as well as various Indian-developed vaccines.

Of the just-over 30 million doses that Cambodia received to inoculate its roughly 16 million population, 27 million doses were of Chinese vaccines, which shows the country's leadership prioritized the rapid execution of its national vaccination campaign by any means over any other considerations. This strategy ultimately proved successful so that Cambodia was able to boast vaccination rates on par with its much wealthier regional counterpart Singapore, as well as open up its economy at roughly the same time as the advanced city state and thus many months ahead of its ASEAN peers.

An August 2021 report noted that "the best vaccine is the one you can get" and that Cambodia was using a mix of Western and Chinese non-mRNA vaccines, including Sinovac, Sinopharm, AstraZeneca and Johnson & Johnson. The same report credits innovations in Cambodia's distribution strategy for its success, noting that a clear and simple ring-fenced distribution plan based on location" rather than more complex to administer age (or risk) tiering allowed Cambodia's vaccination campaign to proceed swiftly, as did the use of the military to support distribution and delivery.

Sources: Khmer Times (2021), McGinley and Higgins (2021), Strangio (2021), Xinhua (2021)

5. Vietnam

The Drug Administration of Vietnam (DAV) is the NRA responsible for the approval and post-market surveillance of drugs, biologics, vaccines and cosmetics and operates under the under the authority of the Ministry of Health.

Similar to other NRAs in the region, Vietnam is active in ASEAN-wide efforts to align regulatory procedures and protocols and uses the ASEAN Common Technical Dossier (ACTD) for approvals and also has a history of relying on previous guidance issued by stringent regulatory authorities, such as the US FDA and the Japanese Pharmaceuticals and Medical Devices Agency (PMDA).

The Vietnamese NRA has performed well in WHO benchmarking reviews of its regulatory capacity. In April 2015 it achieved "Functional" status when audited against the WHO's Vaccine Assessment Tool. Then, following another review in 2018 which further helped the Vietnamese NRA to strengthen its capacity, in 2021 the WHO announced that the DAV had achieved Maturity Level 3, the second highest in the WHO classification of national regulatory systems.

The Vietnamese health authorities were relatively quick to grant emergency use approval to the Oxford-AstraZeneca vaccine, doing so on January 20, 2021, followed by Sputnik V on 23 March. Further approvals followed in June, first for Sinopharm then for the Pfizer-BionTech and then the Moderna vaccines, with the Johnson & Johnson vaccine being approved the following month on 15 July. These approvals were then followed later in the year with further emergency use approvals for the Cuban Abdala and the Indian Covaxin candidates in September and November 2021 respectively.

Despite initial successes in managing the pandemic in 2020, Vietnam's vaccination program was slow to pick up momentum, leaving the country exposed to the Delta variant which arrived in early 2021 and began wreaking havoc by the 2nd and 3rd quarters of the year, with the larger urban centers in oppressive lockdowns which tested the peoples' faith and trust in the government's ability to successfully manage the pandemic.

The government of Vietnam is reported to have placed early orders for the Russian Sputnik V vaccine in August 2020, but effectively began its vaccination campaign – albeit haltingly – only in the second week of March 2021, with a relatively small initial delivery of some 117,600 doses of the AstraZeneca vaccine. Over the course of 2021, and as the country continued to wage a tough battle with the pandemic, donations poured in from across the region and the world, including from the United States, China, Japan, Australia and Italy.

At the time of writing (June 2022), Vietnam, which has vaccinated over 80 percent of its population, has relied predominantly on mRNA vaccines from Pfizer and Moderna, with these making up almost 50 percent of the total of vaccine doses administered, followed by AstraZeneca at almost 30 percent and Sinopharm at almost 25%.

Sources: Nikkei Asia (2021), Wikipedia (2022), Clark (2021).

6. Bangladesh

The Directorate General of Drug Administration (DGDA) is the NRA in Bangladesh responsible for the approval of medicines, including vaccines. The DGDA has regulatory oversight and the ultimate responsibility for implementing the prevailing laws and regulatory frameworks relating to the importation and procurement of both inputs and packaging for pharmaceutical products, as well as the manufacture and import of finished medicinal products, their export, domestic marketing and pricing.

The 2016 Drug Policy recognizes the importance of upgrading the NRA, and explicitly lists this as a priority objective as well as articulating various pathways by which this is to be accomplished, including, appointing professionally qualified and experienced human resources, providing regular training to personnel working in the areas of drug approvals, and the regulation of manufacturing, storage, distribution, sale, import, export and quality control. The 2016 Drug Policy also calls for the human resource development plan, together with the adoption of a career development plan and an internal promotion system based on entirely objective and meritocratic metrics. The explicit goal mentioned here is accreditation with the WHO and membership of the PIC/S.

The DGDA announced emergency use approval for the AstraZeneca vaccine on 5 January 2021, with plans to procure the majority of the country's inoculation needs from the Serum Institute of India. However, when India imposed an export ban on vaccines in March and April of 2021 due to a domestic surge in cases, Bangladesh was forced to begin approving and importing other vaccines, starting first with the Russian Sputnik V vaccine, which was approved on April 27, followed shortly thereafter by China's Sinopharm two days later. By October 2021, Bangladesh had approved 7 vaccines. A domestic candidate, Bangavax developed by Globe Biotech Ltd. was reported to be in clinical trials in Bangladesh, with an approval decision pending the outcome of these trials, but as of the current writing remains unapproved by the DGDA.

As vaccine supplied dried up from India in early 2021, donations from other countries started to pour in, including from the United States, which by February 2022 was the largest single donor to the country, having donated over 61 million doses of the Pfizer and Moderna vaccines. Other countries that donated vaccines to Bangladesh include Japan (AstraZeneca) and China (Sinopharm). Indeed, the DGDA appeared to be tailoring approvals in order to meet announced or incoming vaccine shipments, as it did when it approved the Modern vaccine on 29 June 2021, four days after an announcement that it would receive some 2.5 million doses of the vaccine from COVAX in the next 10 days.

The development of the domestic pharmaceutical industry in Bangladesh has enjoyed significant support from the WHO. In 2016, a coalition of interested partners was

established to support efforts by local manufacturers to meet the requirements of the WHO Prequalification of Medicines Program (PQP). This coalition, worked to coordinate the efforts of development partners, and with technical backstopping from WHO, and under the leadership of DGDA was able to support the country in building local capacity to manufacture and regulate medicines, so that a first PQP approval could be granted in 2019 to Beximco Pharmaceuticals. WHO and DGDA staff conducted GMP inspections together, which again helped strengthen the capacity of the DGDA.

The DGDA has also partnered with the WHO in the context of the organizations Benchmarking Tool, with an interim assessment being conducted in September 2018, with resulted in an institutional development plan being adopted as a roadmap for supporting the DGDA in its efforts to obtain maturity level three, which USAID has also been supporting with training and technical assistance.

Sources: DGDA (2022), Wikipedia, Paul (2021), Dhaka Tribune (2021), WHO (2019).

7. Vanuatu

The Ministry of Health is the organization tasked with the small island nation's vaccine rollout, and does not appear to possess the regulatory capacity to carry out independent approvals of medicines and vaccines. Instead, Vanuatu works closely with the World Health Organization and relies on the WHO's Model List of Essential Medicines.

The first National Medicines Policy for Vanuatu was enacted in 2015 and identifies some eight key objectives, including improvement of medicines regulation and quality. The policy lists as an aspirational goal, that "that medicines to be used in the Republic of Vanuatu (both public and private) should be registered for use." By the same token, the 2015 Policy also articulates the aspiration that "that applicable legislation to regulate the manufacture, importation, exportation, marketing, distribution, prescribing and dispensing and use of medicines will be formulated and implemented". The 2015 Policy commits to working towards these goals, without specifying a timeframe for doing so.

The WHO Country Cooperation Strategy (2018-2022) for Vanuatu lists a number of strategic priorities aimed at improving the regulatory capacity responsible for overseeing and managing the health care system, including to "review, revise and update the health sector policy framework" and "review, develop and update legislation, policies and guidelines in accordance with International Health Regulations (2005).

In terms of the authorities' efforts to vaccinate the population, only two vaccines have been approved for use in Vanuatu, namely AstraZeneca and Sinopharm. This decision was heavily motivated by the ease of storage and distribution of these particular

vaccines, compared to the extensive cold-chain requirements of mRNA vaccines such as Pfizer and Moderna, which are virtually impossible to meet under current conditions in the Western Pacific.

The original planning by Ministry of Health officials released in early 2021 envisaged a slow campaign beginning in April and which would only be complete in 2023 - a relaxed timeline compared with the efforts of many other countries to vaccinate as much of their population as quickly as possible. As it turned out, the campaign was only launched in June of 2021, Reports differ as to current vaccination rate. Reporting by the authorities dated May 2022 indicate that some 75 percent of the population on average had received 2 doses and was thus fully vaccinated. According to these reports, some islands and areas enjoy higher vaccination rates than others, with Port Villa, the capital, boasting a vaccination rate of 92 percent fully vaccinated, while at the other extreme, Tafea is still languishing below 50%. These numbers stand in stark contrast to data published by other sources, with Our World in Data reporting as of 25 April 2022, a vaccination rate of only 38.5 percent.

Sources: Ministry of Health of Vanuatu, WHO, Xinhuanet (2021), McGarry (2021).

8. Australia

The Therapeutic Good Administration (TGA) is the NRA charged with approving medicines (including vaccines) and which took the lead during the COVID-19 pandemic for approvals of various vaccine candidates. Operating under the Australian Department of Health, the TGA regulates the quality, supply and advertising of medicines, pathology devices, medical devices, blood products and most other therapeutics.

The TGA is a stringent regulatory authority that works together with other similarly mature NRAs in the framework of the Access Consortium, comprising (in addition to the TGA), the NRAs from Canada, Singapore, Switzerland and the United Kingdom. Working together through the Consortium, the participating NRAs have successfully completed joint reviews of both innovative and generic medicines and are reported to have received a significant number of expressions of interest from sponsors intending to file through our collaboration pathway.

TGA participates in other international collaborative initiatives in addition to the Access Consortium, including International Coalition of Medicines Regulatory Authorities (ICMRA), International Medical Device Regulators Forum (IMDRF), the International Over-The-Counter (OTC) Medicines Regulators Forum, the International Pharmaceutical Regulators Programme (IPRP), and Project Orbis, an initiative led by the US FDA to provide patients access to promising new cancer treatments.

The TGA is also an important collaborative partner in the region, given its status as a stringent NRA, an example of which is the Pacific Medicines Testing Program which

was launched in 2017 to enhance regional health security. By virtue of this program, the TGA, working with other partners, is piloting a program to provide Pacific Island countries access to Australian laboratory testing for medicines quality assurance undertaken by the TGA's Laboratories Branch. The TGA laboratories have also been designated by the WHO as both a WHO Collaborating Centre for Drug Quality Assurance and a WHO Collaborating Centre for Quality Assurance of Vaccines and other Biologicals.

At the time of writing, the TGA has approved four vaccines for use in the Australian vaccination campaign, which began in February 2021. The Pfizer–BioNTech vaccine was approved on 25 January 2021, with approval of the Oxford–AstraZeneca vaccine following in mid-February. Johnson & Johnson's Janssen vaccine was approved on 25 June 2021 (but is not included in the nationwide vaccination program), and the Moderna vaccine was approved on 9 August 2021.

For the purposes of travel to Australia, the Australian Government recognizes – as per January 2022 – a number of additional vaccines not included in the national vaccination rollout, namely the Chinese vaccines by Sinovac and Sinopharm, the Indian vaccine developed by Bharat Biotech and the Russian Sputnik V vaccine.

Despite what was an initially slow rollout, with Australia languishing at the bottom of the OECD in terms of vaccination rates until the third quarter of 2021, the onslaught of the Delta variant caused the eastern seaboard States of New South Wales and Victoria to abandon their hitherto Covid-zero policies and embark on a race to vaccination, which was also joined by all other States, with various degrees of urgency. At the time of writing, Australia enjoys vaccination rates in excess of 90 percent.

Sources: TGA website, Wikipedia.

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