Appendix to the summary review on vaccine regulatory pathways important for CEPI

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Appendix 1: Regulatory procedures for approval of medicines and harmonisation efforts between regulatory agencies

Table 1. Standard regulatory procedures for product approval

	Summary of standard regulatory procedures
US FDA[1]	All vaccines are regulated as biologics by the Center for Biologics Evaluation and Research (CBER) of the Food and Drug Administration (FDA). A single set of basic regulatory approval criteria apply to all human vaccines, regardless of the technology used to produce them. Authorisation is based on a demonstration of safety, purity and effectiveness, and a determination that the facility and product meet applicable requirements to assure continued safety, purity and effectiveness. Evidence of effectiveness is based on a demonstration of protection against clinical disease or, in some cases, immune response if there is a scientifically well-established immunologic marker to predict protection that can be reliably measured in a validated assay. The legal authority for the regulation of vaccines: Section 351 of the Public Health Service (PHS) Act and from certain sections of the Federal Food, Drug and Cosmetic (FD&C) Act. The PHS Act is implemented through regulations codified in Title 21 of the *Code of Federal Regulations* (CFR), Parts 600 through 680, which contain regulations specifically applicable to vaccines and other biologics. In addition, because a "vaccine" meets the legal definition of a "drug" under the FD&C Act, sponsors must also comply with current Good Manufacturing Practice (cGMPs) regulations in 21 CFR Parts 210 and 211, and, for all human testing prior to authorisation, the Investigational New Drug (IND) regulations in 21 CFR Part 312.
EMA	**Community Marketing Authorisation** **Centralized Procedure** The centralized procedure is undertaken by the European Medicines Agency (EMA). A single application is sent to the EMA and evaluated by its Committee for Medicinal Products for Human Use (CHMP). The final decision is made by the European Commission that issues a marketing authorisation valid throughout the EU, Iceland, Liechtenstein and Norway. The European Medicines Agency's (EMA) scientific guidelines on vaccines assist medicine developers to prepare marketing authorisation applications for human medicines.[2] Once a marketing authorisation is obtained, each batch of vaccines must still be assessed for quality before release for use. This is done by both the manufacturer and an official European control laboratory. The activities of these laboratories are coordinated by the European Pharmacopoeia Secretariat within the European Directorate for Quality of Medicines (EDQM). Vaccines are required to meet additional requirements after-licensing: i) Post-licensure commitments / follow-up measures, e.g. stability studies, further confirmatory safety trials or trials in populations that have not been studied yet, ii) Variations to the original marketing authorisation in order to introduce minor, moderate or major changes to the authorised details of the product, and

	iii) Authorisation renewals, which under European legislations have to be submitted five years after approval. **Orphan designation[3]** Orphan designation of medicines means that manufacturers are eligible to benefit from followings incentives of: assistance with development of the medicine; reduced fees for marketing-authorisation applications; and protection from market competition once the medicine is authorised.[4] To qualify for orphan status there must be: i) intention for the treatment, prevention or diagnosis of a disease that is life-threatening or chronically debilitating; ii) the prevalence in the EU must not be more than 5 in 10,000 or it must be unlikely that marketing of the medicine would generate sufficient returns iii) no satisfactory method of diagnosis, prevention or treatment of the condition concerned has been authorized, or, if such a method exists, the medicine must be of significant benefit to those affected by the condition
Health Canada	**New Drug Submission pathway** (Notice of Compliance) Applicable to all new drugs/vaccines intended for licensure in Canada. A full data package is required.[5]
CFDA/ China	**Regular Authorisation** All vaccine products. A full data package is required.[5]
MHLW Japan[6]	**Regular authorisation** All vaccine products.[5]
Thai FDA/ Thailand	**Regular Authorisation** Imported or local manufactured vaccines.[5]

Table 2a. An overview of some existing accelerated assessment frameworks

	Accelerated assessment frameworks
FDA[7]	**Priority review** Indicates that the medicine treats a serious condition and, if approved, the product has to demonstrate that it would provide significant improvement in safety and/or effectiveness. Assessment basis of safety and/or effectiveness data. Shortened review time (6 rather than 10 months). **Fast track** Indicates that the medicine treats a serious condition and demonstrates the potential to address an unmet medical need. Assessment basis of preclinical and/ or clinical data depending on the development stage. Possible expedited clinical development time due to more intense FDA engagement, with possible staggered submission of marketing application (rolling review). **Breakthrough therapy** Treats a serious condition and preliminary clinical, data demonstrates potential for significant improvement compared with available therapies on a clinically meaningful end point Assessment basis on clinical data. Expedited clinical development time due to intensive discussions between the FDA and sponsor, with organizational commitment of senior staff involvement.
EMA	**Accelerated assessment**[8] This procedure reduces the timeframe for review of an application for marketing **authorisation from a maximum of 210 days to 150 days for medicinal products of major public health interest** and in particular from the viewpoint of therapeutic innovation. Use for medicines of major interest to the public health, particularly those representing a therapeutic innovation. Requires justification by the sponsor of "major public health interest". Can be modified to "normal" assessment if an accelerated assessment is no longer considered appropriate. **Conditional marketing authorisation**[9] For certain categories of medicinal products, the possibility to obtain **a conditional** marketing authorisation on the basis of less comprehensive data than is normally the case and subject to specific obligations and additional comprehensive data to be provided post-authorisation. Conditional marketing authorisations are valid for one year on a renewable basis. Use for seriously debilitating and life-threatening conditions, medicinal product for emergency use, or orphan medicinal products; must address unmet medical need. Assessment basis of non-comprehensive data with little likelihood that there will be timely collection of additional data after the authorisation. Shortened development time **Compassionate use opinion**[10] Opinion by the CHMP defining at European level the criteria and conditions for use of medicinal products which are made available to patients through national patients' access programmes (prior to a marketing authorisation). Article 83 of Regulation (EC) No 726/2004 introduced legal framework for Member State to ask the CHMP when **compassionate use for group of patients** is envisaged to adopt opinions on the conditions for use, conditions for distribution and the patients targeted for a medicinal product in the EU **Marketing Authorisation under exceptional circumstances**[11]

	Article 14 (8) of Regulation (EC) No 726/2004: In exceptional circumstances and following consultation with the applicant, the marketing authorisation may be granted **subject to certain conditions**, in particular relating to the safety of the medicinal product, notification to the competent authorities of any incident relating to its use, and action to be taken. Use for medicines with urgent public health need. Assessment basis non-comprehensive nonclinical and clinical data with little likelihood that it will ever be collected. Shortened development time. Post authorisation data collection, which usually includes an identified program of studies, the results of which form the basis of an annual reassessment of the benefit–risk profile i) indications are so rare that the applicant cannot reasonably be expected to provide comprehensive evidence, or ii) in the present state of scientific knowledge, comprehensive information cannot be provided, iii) it would be contrary to generally accepted principles of medical ethics to collect such information. **Orphan Designation[3]** A status assigned to a medicine intended for use against a rare condition. The medicine must fulfil certain criteria for designation as an orphan medicine so that it can benefit from incentives such as protection from competition once on the market. The following criteria must be met: i) intention for the treatment, prevention or diagnosis of a disease that is life-threatening or chronically debilitating; ii) the prevalence in the EU must not be more than 5 in 10,000 or it must be unlikely that marketing of the medicine would generate sufficient returns; iii) no satisfactory method of diagnosis, prevention or treatment of the condition concerned has been authorized, or, if such a method exists, the medicine must be of significant benefit to those affected by the condition. **Priority Medicines (PRIME)[12]** is a scheme launched by the European Medicines Agency (EMA) to enhance support for the development of medicines that target an unmet medical need. This voluntary scheme is based on enhanced interaction and early dialogue with developers of promising medicines, to optimize development plans and speed up evaluation so these medicines can reach patients earlier. Through PRIME, the EMA offers early and proactive support to medicine developers to optimize the generation of robust data on a medicine's benefits and risks and enable accelerated assessment of medicines applications. PRIME builds on the existing regulatory framework and tools already available such as scientific advice and accelerated assessment. This means that developers of a medicine that benefitted from PRIME can expect to be eligible for accelerated assessment at the time of application for a marketing authorisation.
Health Canada	**Priority Review[13]** Priority review is available for drug submissions for serious or life threatening diseases. A serious, life-threatening or severely debilitating disease or condition for which there is substantial evidence of clinical effectiveness that the drug provides: - effective treatment, prevention or diagnosis of a disease or condition for which no drug is presently marketed in Canada; or - a significant increase in efficacy and/or significant decrease in risk such that the overall benefit/risk profile is improved over existing therapies, preventatives or diagnostic agents for a disease or condition that is not adequately managed by a drug marketed in Canada. A full review is performed within a shortened review time. **Notice of Compliance with Conditions (NOC/c)[14]** (Reduced target timeframe for review) This is applicable for serious, life-threatening or severely debilitating disease or condition for which there is promising evidence of clinical effectiveness based on the available data that the drug has the potential to provide: - effective treatment, prevention or diagnosis of a disease or condition for which no drug is presently marketed in Canada; or

	- a significant increase in efficacy and/or significant decrease in risk such that the overall benefit/risk profile is improved over existing therapies, preventatives or diagnostic agents for a disease or condition that is not adequately managed by a drug marketed in Canada. A prerequisite is the sponsor's written commitment to pursue undertakings, such as carrying out additional clinical trials to verify the anticipated benefit within an agreed upon time frame acceptable to Health Canada. A full review is performed within a shortened review time. At July 2016, Health Canada was running a consultation process to develop an Orphan Drug Regulatory Framework. It will be finalized towards the end of 2016.
MHLW Japan, **Pharmaceuticals and Medical Devises Agency (PMDA)**	In Japan approval schemes can be grouped into 3 categories: application for off-label uses, expedited review for antiterrorism measures, and expedited review.[15] **Orphan Drug[16]** Article 77-2of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals. Could be designated to: i) A vaccine to prevent an infectious disease rarely reported in Japan or that only reported overseas and the use of which is limited to a specific population, such as people who have visited the endemic area. ii) A vaccine to prevent an emerging or re-emerging infectious disease associated with genetic mutation, of which an outbreak has not been reported at the time of designation but which may significantly affect the lives and health of Japanese people, and of which the time and size of epidemic are unpredictable. **Scheme for prompt practical use of unapproved drugs[17]** The extent of products considered for review from the Special Committee on Unapproved Drugs and Drugs Off-label Use Urgently Required for Healthcare has been expanded to include drugs with high medical needs that are unapproved in the West provided they are drugs for serious or life-threatening diseases that satisfy any of the requirements: i) a Phase III clinical trial in Japan initiated by a medical investigator is ongoing or has been completed, ii) excellent study outcome has been published in literatures, etc. and iii) it is applicable to the advanced medical technology B with certain experience, so that practical use of world-first therapeutic drugs may be realized. **Review system for designated for First world products** This is relevant for a drug, etc. to treat a disease, etc. for which the practical application of a ground-breaking treatment is required as soon as possible shall be designated as a world-first product, if it is expected to have marked efficacy and has been developed and applied for in Japan earlier than anywhere else in the world. Subsequently, priority treatment in consultations and reviews shall be given to accelerate realization of practical use. **Expedited approval system for regenerative medical products** To secure timely provision of safe regenerative medicines, a new regulatory framework is needed. After the safety is confirmed and the results predict likely efficacy, the product will be given conditional, time-limited marketing authorisation in order to enable timely provision of the products to patients. - To approve products based on the limited data, such as surrogate endpoints in exploratory study. - Similarity to accelerated approval of USFDA *

	- The product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit It applies to certain new drug products in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments: • Approval based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity. • The drug product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity. • Approval will be subject to the requirement that the applicant study the drug further, to verify and describe its clinical benefit (such as OS). • Post-marketing studies would usually be studies already underway. • FDA may withdraw approval, if a post-marketing clinical study fails to verify clinical benefit. **SAKIGAKE Designation System**[18] This initiative promotes R&D in Japan aiming at early practical application for innovative pharmaceutical products, medical devices, and regenerative medicines.
FDA Thailand	**Fast Track Reviewing Process of New Drugs**[19] For a product of major public health interest, the applicant may request an accelerated/fast track review as laid down in TFDA Regulation. It can reduce the consideration period from 280 working days to 130 working days.
Nigeria (NAFDAC)	Through the NAFDAC indicated interest in the Collaborative Procedure of Registration of WHO Prequalified Medicines.[20] • The collaborative procedure is limited to pharmaceutical products and vaccines that have been assessed and inspected by WHO/PQ. • WHO/PQ and NAFDAC receive applications for the same pharmaceutical product or vaccine. • WHO/PQ, with the agreement of the prequalification holder, shares the full outcome of dossier assessments including the final assessment reports with NAFDAC. • NAFDAC accepts the product documentation in the same format in which they are prepared for the WHO (i.e. CTD). • National regulatory decisions on registration should be issued within 90 calendar days after being given access to the confidential information. • The decision whether or not to register a product remains the prerogative of NAFDAC.
MIT and Singapore (HSA)	**New Drug Development Paradigms (NEWDIGS) initiative**[21] NEWDIGS is a collaborative environment for innovation and learning that takes a systems approach to transforming processes, technologies, and policy elements of innovation. **Adaptive Licensing** NEWDIGS has adopted the approach of taking advantage of an opportunity for proactive, strategic design of policy with broad stakeholder input, followed by the empiric evaluation of these designs to inform discussions about change.

Table 2b. An overview of some emergency procedures

	Emergency use assessments and access procedures
FDA[7]	**Accelerated approval[7]** Relies on the demonstration that a vaccine induces an immune response that is "reasonably likely" to predict clinical benefit, using a surrogate end point (e.g., an immune marker or correlate of protection) or a clinical end point other than survival or irreversible morbidity. Eligible for a medicine that: • treats a **serious condition** • generally provides a meaningful **advantage over available therapies** • demonstrates an **effect on a surrogate endpoint** that is reasonably likely to predict clinical benefit or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality (IMM) that is reasonably likely to predict an effect on IMM or other clinical benefit (i.e., an intermediate clinical endpoint). Requirement: for adequate and well controlled post-marketing study to verify and describe clinical benefit **Approval via the Animal Rule[22]** Allows adequate and well-controlled studies in relevant animal models to provide evidence of effectiveness of the vaccine in humans, if specific criteria are met, including evidence of a clear relationship between the animal study end point and the desired end point in humans (i.e., prevention of EVD or enhanced survival with EVD). It is foreseen —only to those new drug products for which: Definitive human efficacy studies cannot be conducted because it would be unethical to deliberately expose healthy human volunteers to a lethal or permanently disabling toxic biological, chemical, radiological, or nuclear substance; and field trials to study the product's effectiveness after an accidental or hostile exposure have not been feasible. FDA is able to grant a marketing approval in the cases where: i) the human safety of the product has been established, or ii) based on animal efficacy studies when the results of those studies establish that it is reasonably likely to produce clinical benefit in humans. Requirement: Full Chemistry, Manufacturing Controls (CMC) package and human safety data and animal efficacy data. Requirement: Post-marketing studies, such as field studies, to verify and describe clinical benefit and assess safety when such studies are feasible and ethical. **Emergency Use Authorisation (EUA)[23]** Permits FDA to authorize the use of an unapproved medical product or an unapproved use of an approved medical product during an actual or potential emergency. A public health emergency must affect, or have a significant potential to affect, national security or the health and security of US citizens living abroad and involve a biological, chemical, radiological, or nuclear agent or agents, or a disease or condition that may be attributable to such agent or agents. To issue an EUA the FDA must determine that: 1) the agent specified in declaration can cause a serious or life-threatening disease or condition; 2) based on the totality of scientific evidence available it is reasonable to believe that the product may be effective and that the known and potential benefits outweigh the known and potential risks of the product and; 3) there is no adequate, approved, and available alternative to the product.

	In general, the duration of an EUA is limited to the duration of the declared emergency or potential emergency. The use of a product under an EUA is limited to the duration of a declared emergency. It is assessed on a case-by case, depending on a number of factors such as, whether product is approved for another indication, and, in the case of an unapproved product, the stage of development.
EMA	**EMA's accelerated approval pathways**: **Conditional marketing authorisation,**[9] as in the situation of the accelerated procedures. Applies also to medicinal products to be used in emergency situations in response to public health threats recognised either by the WHO or by the Community. **Marketing authorisation under exceptional circumstances.**[11] Same as the accelerated procedures. Both of these regulatory opinions could be used either in the context of an EU marketing authorisation or for a scientific opinion for a so-called Article 58 procedure. See WHO *Collaborative approaches: Article 58.*[11] **Development and approval of medicines for use in the European Union (EU) during pandemics**[24] Once a pandemic has been announced, the EMA implements a pandemic plan, including: - the fast-track review of data for the authorisation of pandemic-influenza vaccines or use in all EU Member States; - continuously monitoring the safety of centrally authorized pandemic-influenza vaccines and antiviral medicines; - recommending changes to the use or authorisation status of these medicines where necessary; - liaising with European partners, including the European Commission , regulatory authorities in EU Member States, agencies such as the European Centre for Disease Prevention and Control (ECDC) , and international partners, such as the World Health Organization (WHO) and regulatory bodies of non-EU countries, to ensure timely exchange of information and co-ordination of activities relating to the pandemic; - communicating relevant information about its activities to the public, healthcare professionals and the media. **Orphan Designation** *(see EMA accelerated and early assessment)*
Health Canada	**Extraordinary Use New Drug Regulations (EUND)**[25] **Restricted to government use once approved.** Drug is intended for: - emergency use in situations where persons have been exposed to a chemical, biological, radiological or nuclear substance and action is required to treat, mitigate or prevent a life-threatening or other serious disease, disorder or abnormal physical state, or its symptoms, that results, or is likely to result, from that exposure, - preventative use in persons who are at risk of exposure to a chemical, biological, radiological or nuclear substance that is potentially lethal or permanently disabling; and - regulatory requirements cannot be met because exposing human volunteers to the substance would be potentially lethal or permanently disabling, and the circumstances in which exposure to the substance occurs are sporadic and infrequent. **Interim Orders**[26] (Time-limited) Case-by-case basis A tool that can be used if immediate action is necessary to deal with an issue and other existing mechanisms are not sufficient to deal with the risk.

	"The Minister of Health may make an interim order that contains any provision that may be contained in a regulation made under the Canadian Food and Drugs Act if the Minister believes that immediate action is required to deal with a significant risk, direct or indirect, to health, safety or the environment" **Special Access Program (SAP)[27]** Provides access to drugs not marketed in Canada for practitioners treating patients with serious or life-threatening conditions when conventional therapies have failed, are unsuitable, or unavailable. Intended for one patient, one physician and one situation. Not intended for first in human use.
CFDA/ China	**Special review and approval procedure** Full market authorisation, prioritized review and shortened review and approval timeline. For the purpose of effective prevention, timely control and elimination of the hazards of public health emergencies to ensure the health and safety of the public.
MHLW Japan, Pharmaceuticals and Medical Devises Agency (PMDA)	**Rapid authorisation of unapproved drugs[17]** This accelerates the practical application of unapproved/off-label use of drugs for serious and life-threatening diseases by expanding the scope of the Council on Unapproved Drugs/Off-label Use to include unapproved in Western countries if it satisfies certain conditions and by improving the environment for companies to undertake development of such drugs.
FDA Thailand	**Emergency Use Authorisation of Medicinal Products (EUA)** (Authorisation is valid only for 2 years) Case by case by risk-benefit assessment Only in the pandemic influenza situation announced by the Ministry of Public Health. Thailand has no other medicinal product or supply to control or prevent the disease in the pandemic influenza situation. The product must be used by the Ministry of Public Health only and must have monitoring system to monitor product safety and efficacy.

Table 3. WHO Prequalification and Emergency Use Assessment and Listing (EUAL) procedure

	WHO Prequalification[28]	Emergency Use Assessment and Listing (EUAL) procedure[29]
WHO	WHO provides a service to UNICEF and other UN agencies for purchase of vaccines, and to determine the acceptability, in principle, of vaccines from different sources for supply to these agencies. There is an established procedure used by WHO for the initial evaluation of candidate vaccines. Reassessment occurs at regular intervals to ensure the continuing quality of vaccines. Principles of WHO prequalification: • Reliance on the WHO-approved NRA (in the manufacturing country) responsible for the regulatory oversight of the manufacture of a vaccine and for certain on-going activities post-authorization. A WHO approved NRA is judged to be "functional for certain vaccine related regulatory functions." • Assurance of production process and quality control (QC) methods that meet international standards. • Production consistency ensured through international good manufacturing practices (GMP) compliance. • Testing for compliance with specifications. • Monitoring of complaints from the field. • Assurance of data to support product safety, efficacy, and country program suitability. There is a prerequisites that the National Regulatory Authority (NRA) responsible for the product is "functional" as per assessment performed using the WHO established indicators. **Collaborative approaches[9]** In collaboration with the European Union (EU), Article 58 of Regulation (EC) No 726/2004[11] allows the Agency's Committee for Medicinal Products for Human Use (CHMP) enables the EMA to give a scientific opinion with the WHO for the evaluation of certain medicinal products for human use intended exclusively outside the EU to prevent or treat diseases of major public health interest. A new product may be eligible for Article 58 under the following pre-conditions: i) vaccines that are or could be used in the WHO Expanded Program on Immunisation, ii) vaccines for protection against a WHO "public health priority disease",	The purpose of this extraordinary procedure is to provide guidance to interested UN procurement agencies and national drug regulatory authorities (NRAs) of relevant WHO Member States. EUAL is a special procedure for vaccines in the case of a public health emergency when the community may be more willing to tolerate less certainty about the efficacy and safety of products, given the morbidity and/or mortality of the disease and the shortfall of treatment and/or prevention options. In such instances, it is paramount to determine the minimal level of information needed for product approval prior to making a product available under a time-limited EUAL, while further data are being gathered and evaluated. To be eligible, the vaccine must meet the following conditions: • The disease for which the vaccine is intended has been declared by the WHO Director-General to be a Public Health Emergency of International Concern (PHEIC). The Director-General may authorize use of this procedure for a public health emergency that does not meet the criteria of a PHEIC if s/he determines that this is in the best interest of public health. • Based on the contingencies of the specific public health emergency, it is reasonable to consider the vaccine for EUAL assessment (e.g., there is no licensed vaccine for the indication or for a critical subpopulation, e.g. children, or there is a specific vaccine shortage). • The vaccine is subject to oversight by a NRA that has been assessed as functional by WHO and is willing to provide oversight of batch release and other post-EUAL product safety and manufacturing quality assurance requirements. • The vaccine is manufactured in compliance with current Good Manufacturing Practices (GMP). If a manufacturer has a documented acceptable history of quality manufacturing of vaccines, WHO may waive the requirement for conducting an on-site inspection.

	iii) vaccines that are part of a WHO-managed stockpile for emergency response iv) medicinal products for WHO target diseases. According to Article 58, the scientific evaluation by the CHMP applies the same standard as for the assessment of EU medicines. Also, the principles of a conditional marketing authorisation, opinion or a marketing authorisation under exceptional circumstances opinion are possible within the Article 58 procedure. The major advantage of the Article 58 procedure lies within the close and early regulatory interaction and alignment of the EMA with the WHO as the directing and coordinating authority on international health within the United Nations, and therefore being the major player in global health crises. Within the Article 58 procedure, the WHO is included from the beginning in the major steps such as the eligibility of the product for the Article 58 procedure, Scientific Advice from the developing company, the scientific evaluation leading to the CHMP opinion and also in post-opinion activities.	• The vaccine applicant attests that it intends to complete the development of the product and apply for WHO prequalification. In the ideal situation, the remaining clinical trials and other requisite testing will already be underway at the time of the application for a EUAL. N.B. A future prequalification application should incorporate all information submitted for the EUAL plus any other information needed to complete a prequalification application. The EUAL process will assess whether, in light of available WHO/international standards, the submitted data demonstrate a reasonable likelihood that the vaccine quality, safety and effectiveness are acceptable, and that the benefits outweigh the foreseeable risks and uncertainties in the context of a PHEIC.

Table 4. Collaborative efforts designed to increase harmonisation and collaboration between National Drug Regulatory Authorities (NRAs)

Organization	Description
AFRICAN Vaccine Regulatory Forum[30]	AVAREF is a regional regulatory network founded by WHO in 2006. AVAREF brings together national regulatory authorities (NRAs) and ethics committees of the countries in the WHO African Region. It currently has 23 members. AVAREF aims to support NRAs in regulatory decision-making. It provides information to countries on vaccine candidates and timelines for clinical trials, and promotes communication and collaboration between African NRAs and ethics committees. It also provides opportunities to bring in the expertise and advice of regulators from Europe and North America – including Health Canada, the European Medicines Agency (EMA) and the United States' Food and Drug Administration (FDA)'s Center for Biologics Evaluation and Research (CBER) – for the benefit of their African counterparts. At the same time AVAREF promotes convergence towards harmonisation of regulatory practices and processes to ensure timely regulatory evaluations and approvals of clinical trial applications and products. Key among AVAREF's achievements has been firstly the establishment of innovative regulatory pathways for clinical trials, secondly the development and use of common guidelines for submission of clinical trial applications, and thirdly the use of joint reviews of multi-country clinical trial applications and joint good clinical practice (GCP) inspections. These strategic forms of collaboration can significantly improve timelines for product development.
WHO R&D Blueprint[31]	The activities of WHO in the area of medicines regulatory support focus on supporting the work of national MRAs. National governments are responsible for establishing strong national medicines regulatory authorities (MRAs) with clear mission, solid legal basis, realistic objectives, appropriate organizational structure, adequate number of qualified staff, sustainable financing, access to up-to-date evidence based technical literature, equipment and information, capacity to exert effective market control. MRAs must be accountable to both the government and the public and their decision-making processes should be transparent. Monitoring and evaluation mechanisms should be built into the regulatory system to assess attainment of established objectives. The role of WHO in the area of medicines regulatory support is two-fold. One aspect relates to the development of internationally recognized norms, standards and guidelines. The second aspect relates to providing guidance, technical assistance and training in order to enable countries to implement global guidelines to meet their specific medicines regulatory environment and needs. WHO established a regulatory networking and support during the Ebola outbreak. WHO's R&D efforts in these areas are part of the overall work on a roadmap – the R&D Blueprint - for better R&D preparedness based on the experience of the R&D work carried out during the West-Africa Ebola outbreak. The roadmap will enable roll-out of an emergency R&D response as early and as efficiently as possible for emerging diseases for which there are no, or few, countermeasures. This has extended beyond the emergency to obtain the necessary follow-up data needed to fully assess the quality, safety and efficacy of each candidate product.
African Network for Drugs Diagnostics and Innovation (ANDi)[32]	In 2011, ANDI was established as a project with intergovernmental status at the African Development Bank (AfDB) and the African Innovation Fund (AIF). It was established to create a sustainable platform for R&D in Africa. WHO /TDR, in conjunction with several African institutions and the African Diaspora, proposed the creation of the African Network for Drugs and Diagnostics Innovation (ANDI). ANDI's chief objective is to promote and support health product R&D led by African institutions for diseases of high prevalence in the Continent. The expected outcome is the discovery, development and delivery of affordable new health tools including those based on traditional medicine, as well as the development of capacity and establishment of centres of research excellence.

	ANDI faces three major challenges. Firstly, there is a significant research gap; very few products are being researched or in clinical trials for the Continent's most prevalent diseases (e.g. malaria, schistosomiasis). Secondly, there is little collaboration between biomedical R&D centers across Africa. This can result in misalignment between research efforts and African needs. Thirdly, there is insufficient investment in African R&D with overall yearly R&D spend of 0.3% of total African GDP, USD 14 billion below the world median. ANDI's role covers three key dimensions : 1) foster the formation of health product R&D networks between African research centers; 2) fund networks for African-led and owned research aligned to local health needs; and 3) advocate for increased investment and priority-driven health product R&D agenda setting.
International Coalition of Medicines Regulatory Authorities (ICMRA)[33]	The ICMRA is a voluntary, executive level, strategic coordinating, advocacy, and leadership entity of national and regional medicines regulatory authorities (MRAs) that work together to provide direction for a range of areas and activities common to many regulatory authorities' missions and goals; identify areas for potential synergies to be made; and, wherever possible, leverage existing efforts to maximize the global regulatory impact. The ICRMA have four over-arching objectives: i) to protect human health throughout the life-cycle of medicinal products; ii) to enable regulatory conditions which facilitate improved access to and availability of safe, efficacious and quality medicinal products. This also includes enabling innovation and advancing regulatory science as it relates to medicinal product research and development; iii) to promote coherent and strategic multilateral cooperation among regulatory authorities, in order to strengthen mutual reliance, trust, synergies and regulatory systems, and to achieve better use of collective resources/work products and sharing of best practices; and to promote the leveraging of regulatory authorities' collective resources, including knowledge and expertise.
ASEAN-Network for Drugs, Diagnostics, Vaccines, and Traditional Medicines Innovation (ASEAN-NDI)[34]	The Association of Southeast Asian Nations (ASEAN) has established the ASEAN-Network for Drugs, Diagnostics, Vaccines, and Traditional Medicines Innovation (ASEAN-NDI). The purpose of ASEAN-NDI is to support R&D innovation to improve access to drugs, diagnostics, vaccines, medical devices and traditional medicine products that address priority public health problems in the region. This is important in the ASEAN region as infectious tropical diseases remain prevalent, emerging, and re-emerging. It was founded in 2009 in line with the objectives of the GSPA-PHI, which include promotion of R&D, development of North–South and South–South partnerships to support capacity building, and establishment of strategic research networks to facilitate better coordination of stakeholders, this will build on limited infrastructure and resources in some countries, which can be addressed by implementing working arrangements among the ASEAN member states, and by sharing resources and expertise. (Montoya). The ASEAN-NDI is envisioned to become Asia's premier facilitator for collaborative innovation in R&D for health products, benefiting primarily the ASEAN but more open to global markets. As a network involving the ten ASEAN member countries, the ASEAN-NDI will Invest in the needed human resources, technological capacity, and financing to ensure sustainable health, development, and security.

The Pacific Alliance[35] (Chile, Colombia, Mexico and Peru)	The Pacific Alliance is a regional integration initiative formed by Chile, Colombia, Mexico, and Peru on April 28, 2011. Its main purpose is for members to form a regional trading bloc and forge stronger economic ties with the Asia-Pacific region. Costa Rica and Panama are candidates to become full members once they meet certain requirements. The United States joined the Alliance in 2013. The United States has free trade agreements with all four countries and has significant trade and foreign policy ties with the region.
PAHO and Pan American Network on Drug Regulatory Harmonisation (PANDRH) [36,37]	An initiative of the national regulatory authorities within the Region, and PAHO, that supports the processes of pharmaceutical regulatory harmonisation in the Americas, within the framework of national and sub-regional health policies and recognizing pre-existing asymmetries.
International Conference of Drug Regulatory Authorities	The International Conference of Drug Regulatory Authorities (ICDRAs) provide drug regulatory authorities of WHO Member States with a forum to meet and discuss ways to strengthen collaboration.
NEWDIGs MIT and Singapore Health Sciences Authority[38]	**New Drug Development Paradigms (NEWDIGS) initiative.** [21] NEWDIGS is a collaborative environment for innovation and learning that takes a systems approach to transforming processes, technologies, and policy elements of innovation. After identifying a high-impact area of need or opportunity within the innovation space, NEWDIGS convenes a sub-team that is interested in this topic and proceeds in a modular fashion **Adaptive Licensing** NEWDIGS has adopted the approach of taking advantage of an opportunity for proactive, strategic design of policy with broad stakeholder input, followed by the empiric evaluation of these designs to inform discussions about change.

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