Deep dive report on the review of provisions and procedures for emergency authorization of medical products for COVID-19 among ICMRA members - July 2021

Disclaimer: This report is meant to inform discussion amongst ICMRA authorities and authorities of other WHO members states on regulatory flexibilities/agilities in the context of COVID-19, other pandemics/emergency situations and routine regulatory conditions. It is not meant to infer WHO or ICMRA endorsement of the examples described herein, including those described in appendices.

1. Introduction

The World Health Organization (WHO) and ICMRA (International Coalition of Medicines Regulatory Authorities) collaborated to collect and review published guidance notes, guidelines and related technical information on regulatory agilities implemented to respond to the COVID-19 challenges. One of the recommendations of the review was to conduct a deep dive into the provisions and procedures for emergency authorisations of medical products for COVID-19 among ICMRA members. This report summarizes data collected from a deep dive questionnaire of participating ICMRA members as well as from other public sources. The report describes similarities, unique features, enablers and limitations associated with emergency use procedures used during the COVID-19 pandemic and presents a number of overall observations (key messages).

This report is intended to complement the output from other ongoing ICMRA projects on the topic of regulatory agilities and inform the work of the newly formed small working group on Regulatory Agilities, Flexibilities and Sustainability (RAFS-WG).

2. Objectives

The objectives of the Emergency Use Authorisation (EUA) deep dive were twofold:

1) Identify examples of agilities that regulators may wish to continue or consider as standard practice or for use in other pandemics, and
2) Identify processes whose outputs could be used for reliance.

3. Scope and limitations

The scope of this EUA Report covers legal provisions and administrative procedures for the emergency or conditional authorisation of medicines, biologics and vaccines for use against COVID-19. Responses received from the regulatory authorities of eleven countries, one region (EU) and the WHO provided information about existing or new measures introduced for the authorisation process. Gaps in information were addressed through on-line research and subsequent verification by participating authorities.

Limitations:

- The findings in this report are based on the subset of ICMRA members who responded to the questionnaire and is not intended to be representative of other regulatory authorities, notably those in low- and middle- income countries (LMIC).
- This version of the report does not include medical devices, such as in-vitro diagnostics, as information received from the survey was limited. Furthermore, responses and documentation tended to focus more on vaccines than therapeutics.
- The questionnaire was not designed to capture experience or lessons learned from measures used to expedite the authorisation of COVID-19 products. It is understood that the RAFS-WG will consider which measures might be suitable for future pandemics or as standard regulatory practice. Notwithstanding the above, the analysis did allow for some observations in this regard.
- The emergency response to COVID-19 in a given country or region considers and includes the authorisation of medical products to diagnose, treat or prevent the disease, the epidemiological situation, the social and historical context and, where available, injury compensation programs. This report is limited in scope to the authorization of medical products for COVID-19.

4. Outputs from the review

The report includes the following components:

A. Summarized facts from responses to EUA Deep Dive questionnaire:

i) Spreadsheet (Part A) presents key information in a tabulated format on regulatory measures introduced and/or used to address the urgent need for medicines, biologics and vaccines to treat or prevent COVID-19.

ii) Narrative summary (Part A) provides further background and context to responses.

B. Analysis:

i) Spreadsheet (Part B) provides an overall analysis of the facts summarized in Part A and presents a high-level country agnostic view of similarities/common approaches; unique features; implementation enablers; implementation limitations and overall observations that inform recommendations.

ii) Narrative overall analysis (Part B) which elaborates on findings from Part B of the spreadsheet.

5. Process and methodology

The review exercise was performed in the following 3 phases between January and July 2021 through virtual meetings:

5.1 Phase 1 – data collection

EUA deep dive questionnaire and guidance circulated to ICMRA members to gather information on the following areas: Country/Region, Regulatory authority, Scope, Name of authorisation, Category, Weblink, Eligibility criteria, Submission and evaluation requirements, Post-approval commitments, Validity, Product status (clinical trial impact), Reliance and use of Certificate of Pharmaceutical Product (CPP).

Responses were collected from 12 March to 9 April 2021. Additional input received following the comment period was also incorporated in the spreadsheet and considered in the analysis.

5.2 Phase 2 - summary and analysis

Review and analysis of responses consisted of the following:

- Preparing a spreadsheet and narrative summary template to capture and analyze information in a standardized form and level of detail. Both documents are divided into Part A–Facts and Part B–Analysis.
  Of note: The spreadsheet provides a greater level of granularity than the original questionnaire and includes a new section related to injury compensation programs.
- Forming a small drafting group to assist in the population and analysis of information. The drafting group consisted of representatives from Health Canada serving (chair), EMA, MHLW/PMDA and WHO (secretariat).
- Sharing draft documents with the respondents to verify the accuracy of information and provide additional updates to Parts A and B as well as the narrative summary.

5.3 Phase 3 – drafting report

Drafting high-level report and revising draft spreadsheet (Appendix 2) and narrative summary (Appendix 3). A list of responding ICMRA member countries/authorities was also included (Appendix 1).

6. Summary of observations

Top-level findings and observations from the review are presented below according to the categories of information collected and analyzed. Please consult the accompanying spreadsheet and narrative summary for a more detailed summary and analysis of information collected.

6.1 General:

- The deep dive exercise generated a comprehensive and authoritative collection of information on provisions and procedures used by respondents to authorize COVID-19 products, including source documents. This collection, together with the presentation of information and findings in a standardized format and level of detail, should serve as a convenient reference for future use.

- All respondents have exercised regulatory agilities in responding to the pandemic. This is underpinned in some countries by special legal authorities or administrative acts specific to COVID-19.
- While the diversity of instruments and measures used reflects specificities of legal and regulatory frameworks, commonalities exist which could inform models and practices for dealing with future pandemics.
- The response to the pandemic also triggered accelerated development of technical and administrative guidance documents and enhanced transparency measures and engagement with product sponsors.
- Findings are consistent with but expand upon those presented in the broader ICMRA-WHO Regulatory Agilities review report.
- Each NRA will have lessons learned to further improve their response during a future pandemic.

6.2 Specific sections:

6.2.1 – Names, types of authorisations and validity conditions

Regulatory authorities approached the regulation of medical products during the COVID-19 pandemic in four different ways:

1) Using existing legislation for approving medicines, including vaccines and biologics
    a. This included conditional marketing authorisation/conditional approval.
2) Using existing legislation in place to allow for emergency use without a marketing authorisation
    a. Under an Act
        i. Policy to allow for emergency use authorisation of COVID-19 vaccines under an existing Act that provides the ability to issue an emergency use authorisation.
        ii. Special approval for emergency use
    b. Under Regulations/Directive
        i. Emergency Use/Compassionate Use articles
        ii. Temporary authorisation
3) Amending existing legislation to accommodate emergency use
    a. Under an Act
        i. Temporary authorisation
    b. Under Regulations
        i. “emergency therapeutic product” through an interim authorisation
        ii. Conditional marketing authorisation
4) Introducing new legal rules to address the emergency use
    a. Interim Order
        i. Temporary emergency authorisation

ii. Submission during specified time period to transition to amended Regulations for a marketing authorisation

b. Decree
   i. Sanitary Authorisation for Emergency Use

c. Ordinance
   i. Exemptions to assure supply of products during the pandemic.

Most jurisdictions have legal provisions for specific, time-limited authorisation approaches applicable to the COVID-19 pandemic. The duration of the authorisation is most commonly fixed at one year and is either linked with

- duration of the emergency situation and the public health needs for the product concerned, affected by changes in the benefit/risk balance of the product concerned, and/or
- the generation of sufficient data for granting of a 'regular' marketing authorisation.

Termination of the authorisation is either though adoption of an administrative act on its revocation, or though expiry.

Similar to the one-year temporary authorisation offered by some NRAs (National Regulatory Authorities), the WHO offers an Emergency Use Listing (EUL) for vaccines, therapeutics and IVDs. The EUL is valid for a period of one year and can be extended, if necessary. While not an authorisation per se, the EUL supports the availability of unauthorised medical products in an emergency situation by facilitating national authorisation schemes based on reliance.

At a basic level, regulatory approaches divide into the issuance of a marketing authorisation or a time-limited legal provision for the use of an unlicensed product. The latter further divides into some form of temporary or emergency authorisation or the waiving of normal market authorisation (MA) requirements, for example, through a ministerial ordinance. These distinctions may have implications with respect to product liability/indemnification, data protection and other legal considerations.

Overall observations: Additional emergency measures taken by countries to provide an authorisation for COVID-19 medicines and vaccines in the context of a pandemic were based on the regulatory environment of the country when the pandemic hit. For some, existing regulatory frameworks could be used, while others needed to develop interim measures quickly. Having a regulatory framework that is poised to address future pandemics would address some limitations encountered with respect to validity and transitioning, consistent with the good regulatory principle of flexibility[1]. Regulatory

[1] WHO Guideline on Good regulatory practices in the regulation of medical products, Annex 11 of Technical Report Series 1033. Accessed: 2021-07-14 https://www.who.int/publications/i/item/55th-report-of-the-who-expert-committee-on-specifications-for-pharmaceutical-preparations

flexibility is a principle of good regulatory practice Optimal benefit requires an appropriate end-to-end framework, preparedness and an evaluation of how well measures met objectives.

6.2.2 - Eligibility criteria and submission, evaluation and authorisation requirements

Regulatory standards were maintained. Flexibilities were exercised in terms of administrative procedures and the timing of data submission based on a science and risk-based approach that considered the severity of the pandemic and a preliminary decision to authorize based on a minimum data package and post-authorisation commitments.

Regulatory authorities who issued an emergency authorisation based their decision on

- reasonable safety, efficacy and quality (S/E/Q) data suggesting that the potential benefits outweigh the known risks when used during the COVID-19 pandemic, and
- there being continuing S/E/Q data generated from ongoing studies to support the eventual transition of the interim/temporary authorisation to full registration/market authorisation.

Most respondents required Phase 3 interim data and provided guidance on a minimum data package to reach a preliminary regulatory decision. During the COVID-19 pandemic, ICMRA, through discussions and workshop activities, acted as a forum for medicine regulatory authorities to discuss data requirements for Phase 3 trials of COVID-19 vaccines.

Early and ongoing engagement with the sponsor is essential to facilitate the product development plan, clarify and address potential regulatory issues and enable the efficient use of resources and timing of data packages (for rolling/progressive review).

Rolling submissions represent an important regulatory tool for reducing the overall time to regulatory decision in the context of an urgent public health need. The rolling review enables a regulator to complete the review of a submission earlier compared to the routine process of starting the review following submission of the full dossier. This type of review is also more complex and resource intensive. Ongoing engagement and planning with the sponsor are important when preparing for, initiating and conducting a rolling submission/review.

A unique regulatory tool introduced during the COVID-19 pandemic was pre-positioning: Pre-positioning is a mechanism for a national public health authority to import a promising COVID-19 drug for placement in facilities before it is authorized. Several conditions must be met, including the manufacturer has filed a submission for the drug's authorization with the NRA but the authorization for the drug has not been issued. Pre-positioning facilitates the immediate distribution of the drug upon authorization.

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Overall observations: There are various responses among regulators depending on situation of their jurisdiction. However, practical requirements are not so different. Leveraging international harmonization between regulators based on data requirements of each jurisdiction as far as possible will enable us to flexibly respond to a new pandemic in the future.

6.2.3 - Post-authorization commitments/ requirements

Post-authorization obligations are established on a case-by-case basis as part of the emergency use or conditional marketing authorization, but at a minimum generally include the following:

- The completion of ongoing and planned studies to confirm the benefit-risk profile
- Post-authorization safety activities as defined in the risk management plan
- The submission of results from ongoing CMC (Chemistry, Manufacturing, and Controls) studies, such as stability data
- Independent batch release by the NRA for vaccines and other biologicals. A number of respondents indicated that this would include testing on all batches. At least one authority has adopted a risk-based approach in terms of lot release requirements.

Most respondents confirmed that post-authorization obligations were legally binding. Non-compliance with conditions could result in revoking the authorization and, where provided, other regulatory actions.

Most authorities also established timelines for the reporting of post-authorization information, with the requirement to report on progress towards meeting targets.

Some of the NRAs mentioned further commitments related to the surveillance of COVID-19 vaccines, notably:

- The filing of monthly safety reports for COVID-19 vaccines in addition to the 6-month PSURs
- Implementation of traceability measures
- Monitoring the impact of new mutations

Overall observations:

- The ability and authority to set and enforce post-authorization obligations are essential to early authorization and availability of COVID-19 products while also ensuring appropriate confirmatory studies and ongoing monitoring to address knowledge gaps.
- While most authorities expect sponsors to apply for a full MA when supported by data the process for doing so differs between countries, reflecting the uniqueness of regulatory environments.
- Transparency of post-authorization obligations and the sharing of information related to ongoing studies are important in promoting greater convergence and more-informed, risk-based

regulatory measures. This is particularly prevalent when regulators rely (in part or full) on other regulatory authorities or WHO.

6.2.4 - Product status/ impact on ongoing placebo controlled clinical trials

Survey responses confirmed that product status (i.e., investigational product or granted MA) did not prevent the continuance of ongoing clinical trials. As noted elsewhere, authorisations have been granted on the basis of interim Phase 3 results with the commitment to confirm the benefit-risk profile through ongoing studies. However, with the increasing deployment of vaccines the feasibility of conducting conventional placebo-controlled trials is in question and has led to active international discussion on alternate designs and requirements for the authorisation of modified and second wave vaccines. Convergence is essential to enabling a rapid and consistent global regulatory approach.

Overall observations: Recognizing that legislation for emergency use differs in each country/region, there is a need to establish a common request for necessary information on the safety and efficacy of COVID-19 vaccines. Placebo-controlled trials are becoming unfeasible. Regulators should discuss/evaluate alternative methods to placebo-controlled trials and harmonize them internationally.

6.2.5 - Reliance provisions and approaches

Based on responses to the questionnaire, regulatory agencies may be divided according to the ability or lack of ability to rely on foreign regulatory authorization for certain elements of review of COVID-19 products. However, the situation is both mixed and nuanced, even for a given respondent. A fuller appreciation of the extent to which reliance and collaboration played a role in the pandemic response requires further discussion and information. Furthermore, information and reports from other regulatory bodies may be used as supportive of reviews even if not used to reduce the extent of review.

Of those authorities and organizations that have an ability to rely on other authorities for the review (or eligibility for emergency authorization) of COVID-19 products, most stipulated the requirement that the reference agency have a ‘comparable/equivalent regulatory system’ or ‘level of control’.

The Prequalification program relies whenever possible on the safety, efficacy and quality evaluations of other internationally recognized regulatory agencies, focusing its efforts on programmatic considerations aimed at ensuring the suitability of products, packaging, labelling and—for medicines and vaccines—pharmacovigilance plans and risk minimization measures in low- and middle-income countries (LMICs). This practice has also been prominent in the emergency use listing of a number of COVID-19 vaccines.

WHO also implemented a global assessment and information-sharing mechanism to expedite national authorisation of COVID-19 vaccines, primarily in LMICs, through reliance on EULs. Key elements included the involvement of geographically selected subject matter experts and the ability of NRAs to access product dossiers and assessment reports through a secure portal based on the consent of

manufacturers and signed confidentiality agreements between WHO and regulators, thereby obviating the need for the filing of product submissions in a majority of countries.

Overall observations:

- While from this study the extent to which reliance played a role in the pandemic response is not fully known (with the exception of WHO), having regulatory provisions enabling reliance, or at least not prohibiting reliance, provides additional tools in addressing the challenges posed by the pandemic. Further retrospective analysis would be needed to determine how provisions and practices could be improved.
- Near real-time information sharing and joint collaboration among regulatory authorities and WHO has been valuable in informing respective regulatory decisions, requirements, communications and plans related to COVID-19 products, notably through ICMRA policy and working groups.
- The EMA's OPEN pilot provided a valuable opportunity to collaborate and contribute to the broader assessment and authorization of COVID-19 products.
- Enhanced transparency measures introduced by a number of regulators to build public confidence in the safety, efficacy and quality of COVID-19 products also serve to promote collaboration, alignment and reliance in the regulatory community.
- The WHO model for global assessment and facilitated in-country authorization has proven successful in accelerating access to quality-assured COVID-19 vaccines, particularly in LMICs.

6.2.6 – Injury compensation programs

Injury compensation programs were not included in the EUA deep dive questionnaire. The working group introduced columns in the spreadsheet to collect data on Party liable for injuries/Party who bears costs. However, on-line research revealed that most of the survey respondents have injury compensation programs for vaccines. Therefore, the columns were renamed Injury compensation program/Administration of compensation. The exception is the European Union where there is no overall vaccine injury compensation program. However, there can be programs at the member state level. The injury compensation programs vary in the way they are administered. For example, Japan has two injury compensation programs, one for the National Immunization Program (NIP) for sufferers from vaccines and one for the conventional compensation programme for therapeutics.

A No-Fault Compensation Program is available to individuals in the 92 AMC countries (Advance Market Commitment) for vaccines supplied through the COVAX Facility.

7. <u>Recommendations and next steps</u>

Recommendations:

7.1 The deep dive exercise generated a wealth of information on provisions and procedures used by respondents to authorize COVID-19 medical products, which together with the accompanying analysis, should serve to inform the work of the RAFS working group. This will require further discussion to assess the effectiveness of measures implemented or not utilized. The outputs of other ICMRA projects related to regulatory agilities, including remote inspection and post-approval CMC changes, will also be important in this regard.

7.2 Related to and illustrative of the above, consider recommendations on how collaboration, transparency and reliance measures could be further enhanced to facilitate convergence, informed regulatory decisions and access to medical products across the international regulatory community. This could also contribute to the ongoing work of WHO good regulatory and good reliance practices.

7.3 Public publication and wide distribution of the report (with the appropriate disclaimers) and possible publication in journal(s).

7.4 Consider addressing the limitations of the current report—including the paucity of information on medical devices (including IVDs), therapeutics and measures implemented by LMICs—as possible follow-on activities. This could include targeted deeps dives and circulation of the report and questionnaire to the broader regulatory community.

Next steps:

7.5 Present to ICMRA Policy group (22 July).

7.6 Seek Policy group endorsement of report and recommendations by 5 August 2021. Adjustments, if required, to be made by the following Policy group meeting.

7.7 EUA Deep Dive Report to serve as input to the RAFS-WG in considering which regulatory practices might be suitable for future pandemics or standard practice.

7.8 Policy group/Executive Committee to confirm any further follow-on work and the responsible working group(s).

8. Appendices

8.1 Appendix 1: List of responding countries/authorities

8.2 Appendix 2: EUA Deep Dive Tabulated Summary

8.3 Appendix 3: EUA Deep Dive Narrative Summary

9. Contributors

ICMRA representatives:

- Ruth Hansson (Chair), Health Canada – Canada
- Mika Togashi, Pharmaceutical and Medical Device Agency – Japan

- Mr Naoyuki Yasuda, Ministry of Health, Labor, and Welfare – Japan
- Zigmārs Sebris, European Medicines Agency – European Union
- Dr Irene Rager, European Medicines Agency – European Union
- Martin Harvey Allchurch, European Medicines Agency – European Union

WHO/Department of Regulation and Prequalification

- Mr Deusdedit Mubangizi
- Dr Razieh Ostad Ali Dehaghi

Secretariat

- Mr Mario Musonda
- Mr Mike Ward

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Appendix 1: List of responding countries/authorities

SN	Country/Region	Authority/Source
1	Canada	Health Canada – HC
2	China	National Medical Products Administration – NMPA
3	Colombia	Instituto Nacional de Vigilancia de Medicamentos y Alimentos – INVIMA
4	European Union	European Medicines Agency – EMA
5	Germany	Paul-Ehrlich-Institut – PEI
6	Japan	Ministry of Health, Labour and Welfare/ Pharmaceutical and Medical Devices Agency (MHLW/PMDA)
7	Kingdom of Saudi Arabia	Saudi Food and Drug Authority – SFDA
8	Republic of Korea	Ministry of Food and Drug Safety – MFDS
9	Singapore	Health Sciences Authority – HSA
10	Switzerland	Swissmedic
11	United Kingdom	Medicines and Healthcare products Regulatory Agency – MHRA
12	United States of America	United States Food and Drug Administration – FDA
13	World Health Organization	Regulation and Prequalification Department – RPQ

Appendix 2 - Emergency Approvals

Country/Region	Authority	Legal provisions for Emergency approval	Name and type of authorisation	Types of products included (specify)	Validity/Duration (and renewal)	Mechanism for termination	Eligibility Criteria	Differences in technical requirements and procedures from usual (full) MA pathway					Requirements for authorisation	Post authorization requirements:					Ability to rely on foreign regulatory authorization for certain elements of review (Y/N - describe)	Injury compensation program	Administration of compensation
								Decision based on minimum S/E/Q data to conclude positive B/R (Y/N - describe)	Provision for rolling/progressive review (Y/N)	Enhanced discussions with sponsors (Y/N - describe)	Enhanced transparency measures (Y/N - describe)	Other (describe)		Nature of obligations: legally binding (Y/N)	Commitment to complete studies for full MA (Y/N)	Safety monitoring (Y/N - describe)	Batch testing (Y/N - describe)	Other (describe)			
Canada	HC	Yes. Interim Order Respecting the Importation, Sale and Advertising of Drugs for Use in Relation to COVID-19	Temporary emergency authorization	• Prescription and non-prescription professional use pharmaceuticals • Radiopharmaceuticals • Biologically-derived products such as vaccines, blood derived products, and products produced through biotechnology • Veterinary drugs	The interim order expires on September 16, 2021. At that time, all authorizations issued under the IO will also expire. However, the manufacturer can file a submission under the amended *Food and Drug Regulations* within specified timelines to transfer the authorization to the regulations. If a submission is not filed within specified timelines, then the authorization will be revoked.	Expiry of the Interim Order; • Not meeting specified timelines for making a submission to transition under the *Food and Drug Regulations* ; or • Issuance of a Notice of Compliance under the *Food and Drug Regulations* • Failure to comply with terms and conditions of licence	A COVID-19 drug is a drug that is manufactured, sold or represented for use in relation to COVID-19.	Yes. S/E/Q data may not be as comprehensive as that of a typical drug submission. Authorizations under the Interim Order will be granted only if Health Canada determines that the B/R of the product are supported by evidence that the drug is safe, effective and of high quality. This takes into consideration the uncertainties related to the drug in the context of an urgent public health need related to COVID-19.	Yes (rolling review). The applicant must include an Application Plan describing studies to be completed and timing of planned submission to Health Canada.	Yes. (1) Early and ongoing discussions with sponsors strongly encouraged to ensure regulatory requirements are met. (2) Applicants are also encouraged to have regular communications with Health Canada. (3) Sponsors are encouraged to contact Health Canada for discussions and meetings specifically related to the topic of product labelling.	Yes. As decisions are made/submissions are received, they are published on Government of Canada website: (1) List of Applications Received (2) List of Drugs Authorized (3) List of Foreign Drugs in Relation to the COVID-19 Pandemic (not used) (4) List of New Drugs for Expanded Indication Expedited publication of the rationale for decision, information related to safety issues and publication of clinical data. Creation of new tools including dedicated web pages for approved vaccines to describe the decision, use and post-market monitoring and a dedicated regulatory 'portal' where all regulatory documents and departmental announcements are housed		(1) application meets requirements of IO (2) all additional requested information and material is submitted to HC (3) sufficient evidence supports benefits of COVID-19 drug; the benefits outweigh risks; applicant has commmited to additional measures needed to mitigate risks and address information gaps taking into consideration the uncertainties related to the drug in the context of an UPHN related to COVID-19	Yes. Terms and conditions can be imposed or amended on an authorization.	No. The authorization expires unless the sponsor files a submission under the amended *Food and Drug Regulations* within a specified time period. If the sponsor files the submission under the FDR, there would be terms and conditions under the *Regulations* to complete.	Yes. The same safety and effectiveness monitoring as with all drugs.	Yes. Health Canada's Lot Release Program categorizes lots of COVID-19 vaccine as Group 3 with different requirements depending on the product. Based on the outcomes of the review some sponsors are required to notify Health Canada of the lots to be distributed to Canada, supply a COA (Certificate of Analysis) and the number of doses. Other sponsors required a lot release letter following protocol review prior to distribution.		The ISAD IO provides for the authorization of a drug based on certain elements being authorized by a foreign regulatory authority. This provision was not introduced into the *Food and Drug Regulations* . However, the use of foreign reviews, where appropriate, continue to perform part of the evaluation or to inform Health Canada's decision-making. Collaborative review with international regulatory partners is possible in cases where manufacturers file a rolling submission simultaneously with HC and another jurisdiction with which there is a collaborative agreement (see also under Switzerland regarding the work-sharing initiative of the Access Consortium). HC is also participating in the EMA's OPEN pilot.	• Pan-Canadian no-fault Vaccine Injury Support Program • Québec, Vaccine Injury Compensation Program	• A third-party administrator administers the program and manages financial support payments through a 5-year Contribution Agreement with the Public Health Agency of Canada. • Through an agreement with Québec's Minister of Health and Social Services, the Société de l'assurance automobile du Québec (SAAQ) calculates and pays compensation to cases who obtain favourable decisions.
Canada	HC	Yes. (1) Interim order respecting the importation and sale of medical devices for use in relation to COVID-19 and (2) Interim Order No. 2 Respecting the importation and Sale of Medical Devices for Use in Relation to COVID-19	Interim authorizations	All 4 classes of medical devices are eligible, provided that they can identify their direct use for COVID-19 and are required as a matter of urgent public health need // Expanded use authorizations are being given for new indications for devices already marketed in Canada	Interim authorization for a period of one year; Interim Order No. 2 expires on March 1, 2022.	1) Expiry of Interim Order; 2) Cancellation of interim authorization due to a safety, effectiveness or quality issue; 3) Cancellation of interim order authorization due to manufacturer receiving a medical device licence under the *Medical Devices Regulations* .	All 4 classes of medical devices are eligible, provided that they can identify their direct use for COVID-19 and are required as a matter of urgent public health need // Expanded use authorizations are being given for new indications for devices already marketed in Canada	Yes. Safety, effectiveness and quality information are not as comprehensive as a standard medical device licence application. Authorizations under the Interim Order will be granted only if Health Canada determines that the benefits and risk of the device are supported by sufficient evidence, when taking into consideration the uncertainties related to the device in the context of urgent public health need.	No, no rolling review.	No, enhanced discussions with manufacturers are not undertaken as a regular part of the authorization and/or marketing process.	Yes. Four lists published and amended from time to time on the Government of Canada website: 1) List of authorized testing devices; 2) List of authorized non-testing devices; 3) List of medical devices for expanded use; and 4) List of products no longer authorized under the IO.		(1) application meets requirements of IO (2) all additional requested information and material is submitted to HC (3) sufficient evidence supports benefits of COVID-19 medical device; the benefits outweigh risks, having regard to the uncertainties relating to the benefits and risks and the urgent public health need; manufacturer has committed to post-market monitoring (for all authorizations) and terms and conditions (for some authorizations).	Yes. Terms and conditions imposed or amended on an authorization are legally binding.	No. Manufacturers are not required to complete all terms and conditions (including studies) in order to receive a full licence under the Medical Devices Regulations. Terms and conditions can carry over as necessary.	Yes, manufacturer commits to the same safety monitoring as all other medical devices (incidents, complaint handling, distribution records and recall procedures in place).	No.				
China	NMPA	"Administrative Measures for Drug Registration" (No. 46 of 2020)	Conditional marketing authorization	Medicines; vaccines; medical devices/in vitro diagnostics	Validity is case-by-case and depends on the duration required to complete the post approval commitments.		1. Drugs that are used to treat serious and life-threatening diseases and for which no effective treatment(s) is available, and drugs urgently needed for public health, and whose clinical trials have already shown their efficacy and whose clinical value can be predicted. 2. Vaccines that are urgently needed in response to major public health emergencies or other vaccines that are identified as being urgently needed by the National Health Commission, whose benefits are evaluated to outweigh risks.	Yes. Clinical data show that the benefits outweigh the risks, one of the five conditions can be met.	Yes (rolling review)	Yes. Applicants should communicate with the Drug Evaluation Center regarding the clinical trial design and clinical trial results that support conditional approval. Applicants are encouraged to communicate before carrying out clinical trials and before applying for conditional approval for marketing.			Vaccines urgently needed in response to major public health emergencies based on the analysis data of the phase III clinical trial may be approved for marketing with conditions if the benefits are greater than the risks. The MAH must carry out new or ongoing clinical trials in accordance with the specific conditions attached to the drug registration certificate.	Yes.	Yes. MAH must carry out new or ongoing clinical trials in accordance with the specific conditions attached to the drug registration certificate to confirm the expected clinical benefits. Should include at least the following: post-marketing clinical research plan, study completion date, final clinical research report submission date.	Yes. The MAH shall take corresponding risk management actions for existing or identified risks and potential risks based on the established post-marketing risk management plan.			No.	Yes.	
Colombia	INVIMA	Decree 1787 of 2020	Sanitary Authorization for Emergency Use (ASUE)	Medicines required during a health emergency	Validity is for one year. It may be renewed only once for the same term.	Terms and conditions indicated in the Decree 1787 of 2020	Differ depending on the requirements that are met for the drug. Eligibility for ASUE: Chemical synthesis or biological drugs that do not yet have all the information required for obtaining the sanitary registration (MA) and are intended for the diagnosis, prevention or treatment of Covid-19. Includes new drugs or those that having a MA in relation to a second indication for unsatisfied therapeutic needs generated by Covid-19.	Yes. Ongoing clinical study, and data which allows INVIMA to conclude that the benefit-risk balance is favorable.	Yes (progressive review). At filing, must include Modules 1 and 2 of CTD.	Yes. Manufacturers interested in obtaining an Emergency Use Sanitary Authorization may request a meeting with INVIMA, meetings prior to the filing of the application. Objectives include to plan and optimize the procedure in order to improve the capacity for review; facilitate technical and scientific interaction; and verify the development status.			Positive benefit/risk profile and compliance with conditions set by INVIMA including completion of ongoing studies, RMP and PV strategies.	Yes.	Yes. MAHs granted ASUE are expected to complete ongoing studies and those requested by INVIMA to confirm a favorable benefit-risk balance of the product and obtain a sanitary registration (marketing authorization).	Yes. The MAH must also comply with the risk management plans and pharmacovigilance strategies approved by INVIMA.			Yes. Reliance on recognized authorities and institutions may be full or partial: - GMP certification: full - Issuance of ASUE: partial or full. Recognized regulatory Authorities/agencies: Argentina, Brazil, Canada, Denmark, France, Germany, Japan, Netherlands, Norward, Sweden, Switzerland, United Kingdom, USA and the EMA.	Yes, in Colombia there is a program for compensation for injuries contemplated in Law 2064 of 2020, which details the form of compensation in accordance with the evaluation against the cause of the damage.	
EU	EC/EMA	No, but specific provisions for this authorization apply in public health emergencies	Conditional marketing authorisation	Medicines (including vaccines and other biologicals) addressing unmet medical needs, including products for use in public health emergency	Valid for 1 year, renewable	Conversion to a standard MA or withdrawal/ revocation/ non-renewal	Product addressing unmet medical needs, including in the context of public health emergencies	Yes. Fast-track review and approval, based on less comprehensive S/E/Q (clinical, non-clinical and/or quality) data than normally required. The available data must support a positive benefit/risk profile and that applicant is able to provide the comprehensive clinical data in the future (see criteria).	Yes (rolling review is being applied in public health emergency context; no explict provision in the legislation)	Yes. Enhanced dialogue with sponsors from very early stage through to assessment and post-approval is being applies in public health emergency (no explicit provision in the legislation).	Yes. Standard EMA transparency provisions apply to all marketing authorisations. Additional transparency measures in place as part of COVID-19 response, including information on vaccines and therapeutics that have received scientific advice, are under rolling review, safety updates, etc.	Normally only the clinical data can be less comprehensive than normally required, but in case of a public health emergency also the non-clinical and/or quality (pharmaceutical) data may be less comprehensive	(a) the benefit-risk balance of the medicine is positive; (b) it is likely that the applicant will be able to provide comprehensive data post-authorisation; (c) the medicine fulfils an unmet medical need; (d) the benefit of the medicine's immediate availability to patients is greater than the risk inherent in the fact that additional data are still required.	Yes.	Yes.	Yes (pharmacovigilance requirements as for any MA apply + additional monitoring can be required as part of specific obligations)	Yes (standard EU manufacturing and batch testing requirements apply.	Conditional marketing authorisation includes specific legally-binding post-authorisation obligations. EC/EMA have authority to take regulatory actions, including revocation of conditional marketing authorisation, in case of non-compliance and potentially levying of fines.	No (except GMP status recognition under MRAs, as for any MA). EMA initiated the OPEN pilot in December 2020 to increase international collaboration on the evaluation of COVID-19 vaccines and therapeutics.	Marketing authorisation holder (liability regime same as for other MAs)	Standard requirements on sponsor, applicant or marketing authorisation holder. EMA offers free scientific advice for COVID-19 products.

Country/Region	Authority	Legal provisions for Emergency approval	Name and type of authorisation	Types of products included (specify)	Validity/Duration (and renewal)	Mechanism for termination	Eligibility Criteria	Differences in technical requirements and procedures from usual (full) MA pathway					Requirements for authorisation	Post authorization requirements:					Ability to rely on foreign regulatory authorization for certain elements of review (Y/N - describe)	Injury compensation program	Administration of compensation
EU	EU NCA	Yes	Emergency use (Art 5.2 of Directive 2001/83/EC)	Medicines (including vaccines and other biologicals)	Defined at national level (expected not to exceed duration of the emergency)	Defined at national level (but expected to stops when MA granted)	Unauthorised medicinal product for use in response to the suspected or confirmed spread of pathogenic agents, toxins, chemical agents or nuclear radiation any of which could cause harm	The requirements for (strength of) demonstration of B/R balance not defined at EU level - decision taken at national level, but may be supported by a scientific opinion from EMA (if requested). Less data than for a (conditional) MA may be acceptable.	May exist at national level, but has not been used at EU level. This route may be available based on limited data (stepwise assessment may be less important).	Normally plans for such use are discussed at national level. For COVID-19 products EMA is open to engage with all developers irrespective of the regulatory route intended	Mostly done at national level. If such use is supported by a scientific opinion from EMA, this information is published	Granting of such exemption for supply of unauthorised medicine falls in the national competence. As EMA may be asked to provide opinion on any scientific matter, national decision may be supported by an EMA opinion (but this is not required).	Criteria set at national level and case-by-case approach may be applied depending on the particular circumstances of the public health emergency	Not foreseen at EU level	No (this authorisation can not be converted into a 'regular' or conditional MA)	Not regulated at EU level (may be required at national level)	Not regulated at EU level (may be required at national level; generally expected)		Not explicitly foreseen (but not excluded for national decision making)	Only very limited exemption from liability for the company	not defined at EU level (it's understood that normally Member States pay to obtain such product's)
EU	EMA or NCA	Yes	Compassionate use	Unauthorised medicines	Undefined	Stops when MA granted (but patients already included can continue to receive the product)	Medicines eligible for centralised procedure (primarily innovative medicines) for use in patients with a chronically or seriously debilitating disease or whose disease is considered to be life-threatening, and who can not be treated satisfactorily by an authorised medicinal product	Less data than for a (conditional) MA may be accepted.	Although updates to compassionate use programmes/opinion are possible, normally stepwise data submission for compassionate use programmes is not used	Normally plans for such use are discussed at national level. For COVID-19 products EMA is open to engage with all developers irrespective of the regulatory route intended	Mostly done at national level. If such use is supported by a scientific opinion from EMA, this information is published	Compassionate use programmes are authorised at national level, but in case a programme is run in several MSs it would often supported by EMA opinion with recommended conditions for use of the product under compassionate use	All available evidence to be reviewed that can support use in patient without available treatment alternatives and not included in clinical trials, on a compassionate basis. For efficacy may rely on promising early data observed in exploratory trials.	Certain conditions may be recommended for compassionate use programmes to be imposed at national level, but scope of obligations normally more limited than for a conditional MA	No (this authorisation can not be converted into a 'regular' or conditional MA)	Yes (mandatory at EU level is supported by EMA opinion, may be required nationally in other cases)	Not regulated at EU level (may be required at national level; generally expected)		Not explicitly foreseen (not used for EMA opinions, when requested)	with prescriber	not defined at EU level (it's understood that at least in some cases the companies are paid to provide the product)
Germany	PEI	Ordinance assuring the supply of products for medical needs for the population in the context of the epidemic caused by the coronavirus SARS-CoV-2 (MedBVSV)	Ministerial supply	Medicines, vaccines, medical devices/in vitro diagnostics	The applicability of the MedBVSV is limited in time. It ceases to be in effect when the German Bundestag declares the epidemic situation of national importance to be over. The temporary supply/placing on the market of medicinal products without market authorisation based on the MedBVSV is no longer possible as of the date the MedBVSV ceases to be effective. *Validity depends on the duration required to complete the post approval commitments (Case by case)*	Conditional MA ceases to be in effect when the MedBVSV ceases to be effective.	Includes vaccines and biomedicines. All products for medical needs that are necessary for the supply of the population during the epidemic situation. NRA provides an opinion/assessment report.	After liaising with the ministry of health, the manufacturer submits to NRA documents relating to information on S/E/Q for evaluation.	No.	Yes. Manufacturer liaises with Ministry of Health prior to submitting S/E/Q documents.	No.	The evaluation the German NRA is obliged to perform according to the MedBVSV has to be a full evaluation of all available data. Assessment reports, certificates etc. from other NRAs can be used as supporting documentation.	(1) The supply and placing on the market by the Ministry of Health is only permitted if the quality of the medicinal product is guaranteed and a positive B/R ratio can be expected. 2) An exemption from the obligation to obtain an MA can be granted by the NRA in individual cases, after a B/R assessment has been carried out and if this exemption is necessary to ensure the supply of medicines to the population.			For the medicinal products without a marketing authorization that are distributed/placed on the market based on the MedBVSV in accordance with the aforementioned criteria all pharmacovigilance provisions of the German Medicinal Products Act apply without exception.	Yes. The NRA usually performs batch testing for specific products, e.g. vaccines		Assessment reports, certificates etc. from other NRAs can be used as supporting documentation.	Yes.	
Japan	MHLW/PMDA	Yes, under Article 14-3 of the *Pharmaceuticals and Medical Devices (PMD) Act*	Special Approval for Emergency (SAE)	Therapeutics, vaccines, medical devices and diagnostics	Valid until the Minister for Health, Labour and Welfare withdraws the approval	Conditions triggering SAE no longer persist or withdrawal is necessary to prevent damage to public health	1. Emergency situation requires an unapproved medical product to be used to prevent damage to the public health caused by the spread of diseases, 2. Emergency situation cannot be managed appropriately by any means other than the use of the unapproved product, and 3. Product is legally available in a country with regulatory system for medical products that is equivalent to Japan.	Yes. Requirements for vaccines described in the "Principles for the Evaluation of Vaccines Against the Novel Coronavirus SARS-CoV-2".	No. No rolling review	No. But, PMDA encourages the applicant to communicate and use scientific advice system.	Yes. After the SAE, the fact is open through PMDA HP.		Submission requirements are same as general approval. However, data set for the submission other than those concerning test results of clinical studies may be suspended (for a reasonable time).	Yes. SAE can request approval holder condition after the approval	Yes. Long-term follow-up results of a large-scale clinical studies and new clinical trials must be reported by the manufacturer to PMDA and publicized.	Yes. The MAH must take appropriate post-marketing actions for safety based on the safety information obtained from the clinical studies.	Yes. All the lots must be tested for quality assurance		SAE activation requires the product to be legally available in a country with a regulatory system for medical products that is equivalent to Japan through designation by the Cabinet Order for SAE. For COVID-19 related medicines, including vaccines and biologics, the following countries were designated: USA, UK, Canada, Germany, France.	Relief services established by government for injury for vaccine and adverse health effects for therapeutics, including COVID-19 products approved as SAE.	Vaccines: Injury to health service (MHLW) funded by government with contribution from MAH. Therapeutics: Adverse health effects service (PMDA) funded by government with contribution from MAH.
Japan	MHLW/PMDA	https://www.pmda.go.jp/files/000235010.pdf	Priority Review	Therapeutics, vaccines, medical devices and diagnostics	Validity is same as general approval	N/A	For the medical products to be used against COVID-19 with prior consultation.	Same as general approval	No. No rolling review	No. But, PMDA encourages the applicant to communicate and use scientific advice system.	Yes. After the approval, the fact is open through PMDA HP.		Submission requirements are same as general approval. MHLW/PMDA evaluate/ investigate its application with the highest priority.	Certain conditions may be recommended for compassionate use programmes to be imposed at national level, but scope of obligations normally more limited than for a conditional MA.	Post approval requirements are same as general approval.	Post approval requirements are same as general approval.	Post approval requirements are same as general approval.		None	Same as general approval	Same as general approval
K. Saudi Arabia	SFDA		Conditional approval	Medicines and vaccines for the prevention or treatment of COVID-19	Not applicable		Medicines and vaccines for the prevention or treatment of COVID-19	Yes. I. Chemistry, Manufacturing, and Controls Requirements II. Safety and Effectiveness Requirements III. Administrative/General Requirements	Yes. Rolling submission	Yes. Encourages companies to communicate with SFDA for any update and to answer any questions. SFDA asks the companies to arrange a meeting before applying for the conditional approval for marketing.	Yes. https://sfda.gov.sa/en/covid-19 https://sfda.gov.sa/en/node/66120 https://old.sfda.gov.sa/en/medicaldevices/regulations/Documents/SFDA-MD-Covid19en.pdf				Commitments to complete all requirements.						
Rep. Korea	MFDS	No. *Regulation on approval and review of biological products*, MFDS Notification No.2021-29, Article 41 (Fast Track review, etc.)	Conditional market authorisation	Medicines (biologicals) and vaccines	5 years (can be renewed)		Pharmaceuticals that may have preventive or therapeutic effects against bioterrorism infectious disease and other pandemic.	Yes. Article 41 allows the submission of some documents required after product approval and the review to approve through the fast track process preferentially.	Yes. Rolling submission							Yes. Continued monitoring of safety and effectiveness. Safety monitoring and activities as defined in the RMP		Submission of results from ongoing studies.		Yes.	
Singapore	Health Sciences Authority	Yes. Pandemic Special Access Route (PSAR), "emergency therapeutic product" through an interim authorisation under sub regulations 6DA(4) and (5)(b) of the *Health Product (Therapeutic Products) Regulations*.	Interim authorization	For designated health products which the Government of Singapore requires during a pandemic: novel therapeutics and vaccines may be designated by the Health Minister as an "emergency therapeutic product."	Companies are required to file an application to transition the product from the PSAR interim authorisation to a full registration, once sufficient data is available.	The HSA can terminate the interim authorisation if any of the following occurs: - evolving Q/S/E data shows suggests benefits no longer outweigh the risks - emergency has ceased - adequate Q/S/E data supports a registration application to transition emergency therapeutic product to a registered therapeutic product	For designated health products which the Government of Singapore requires during a pandemic.	) there is reasonable quality, safety and efficacy (QSE) data suggesting that the potential benefits outweigh the known risks when used during the COVID-19 pandemic; and ii) there is continuing QSE data generated from ongoing studies to support the eventual transition of the interim authorisation to full registration.	Yes. Rolling submission	Yes. Pre-submission meeting to discuss data submission plan.	Yes. List of emergency therapeutic products granted interim authorisation via the PSAR.				Yes. Authorization under PSAR considered if there is continuing QSE data generated from ongoing studies to support the eventual transition of the interim authorisation to full registration.	Submission of Q/S/E data generated from ongoing studies as well as periodic reporting on real world safety and effectiveness to HSA.				Yes. Vaccine Injury Financial Assistance Programme for COVID-19 Vaccination (VIFAP)	

Country/Region	Authority	Legal provisions for Emergency approval	Name and type of authorisation	Types of products included (specify)	Validity/Duration (and renewal)	Mechanism for termination	Eligibility Criteria	Differences in technical requirements and procedures from usual (full) MA pathway					Requirements for authorisation	Post authorization requirements:					Ability to rely on foreign regulatory authorization for certain elements of review (Y/N - describe)	Injury compensation program	Administration of compensation
Switzerland	Swissmedic	Yes. Temporary authorisation to use medicinal products in accordance with Article 9b para as a part of revision of the *Therapeutic Products Act* .	Temporary authorisation	New active substance that cumulatively meets the criteria to qualify as a human medicinal product for temporary authorization. (See column H.)	• Maximum of two years. • Conversion to an ordinary authorisation is contingent on fulfillment of the conditions imposed. • All documentation on the fulfilment of conditions must be submitted to Swissmedic for review within two years of the official approval decision for the temporary authorisation, together with an application for the granting of ordinary authorisation. (An ordinary authorisation is valid for five years.)	At the same time as the documentation on the fulfilment of conditions, the authorisation holder must also submit an application for converting the temp.auth. into an ordinary authorisation.	a. The product is used "to identify, prevent or treat a disease that can lead to serious invalidity, severe suffering possibly resulting in death or to the death of a patient in the short term." b. No alternative and equivalent medicinal product is authorised in Switzerland. c. Major therapeutic benefit is expected from use of the product for which authorisation is being requested. d. The applicant is expected to be able to supply the necessary data per section 2 of the TPLO before the temporary authorisation expires with a view to achieving ordinary authorisation. e. It takes so long to compile all the required data and to process and evaluate the data under letter d in an ordinary authorisation procedure as per Art. 11 TPA that irreversible damage in patients would result or worsen or this would be associated with severe suffering.	Temporary authorisation due to clinical data being incomplete at the time the authorisation was assessed. Temporary authorisation is contingent on the timely fulfillment of conditions.	No.	Yes. Scientific Advice meeting and then a Pre-submission Advice meeting.	Yes. Coronavirus disease (COVID-19) Pandemic page provides Product information, guidance document, questions and answers and animated videos (All about the vaccines - briefly and concisely explained.)			Applicants granted a temporary authorisation are expected to convert to an ordinary authorisation contingent on the fulfilment of the conditions imposed for the temporary authorisation.	Specific conditions regarding safety specifications, the further collection of pharmacovigilance data and implementation of risk mitigation measures may be imposed.			Yes. Application of Article 13 TPA. For medicinal products already authorised in a country with a comparable control system, Swissmedic, at the request of the applicant, will take into account the assessment results of the reference authority. Reduced assessment is also possible for an application for temporary authorisation if certain conditions are met. It is also possible to ask for an authorisation application to be reviewed within the framework of the work-sharing initiative of the Access Consortium.	Yes.	
UK	MHRA	Yes. Temporary authorisation. Article 174 Human Medicines Regulations 2012 and Article 174A Human Medicines (Coronavirus and Influenza) (Amendment) Regulations 2020 (SI 2020/1125)	Temporary authorisation	Medicinal product, such as a COVID-19 vaccine	Valid until expressly withdrawn by MHRA or upon issue of a full market authorisation by the MHRA.	R174 temporary authorisation is valid until it is either expressly withdrawn by the MHRA or the MHRA issues a full marketing authorisation (MA)	The Licensing Authority needs to be satisfied that there is sufficient evidence to demonstrate the safety, quality and efficacy of a vaccine before it will consider issuing an R174 temporary authorisation for the supply of a vaccine.	Yes. The requirements for a UK Regulation 174 emergency approval are very similar to the requirements for a conditional market authorisation. In both cases there needs to be sufficient data on quality, safety and efficacy to conclude that the risk/benefit analysis is positive.	Yes. Rolling review		Yes. • Regulation 174 approval information, Conditions of authorisation, and Public Assessment Report/Summary for each vaccine approved through that path is available on the GOV.UK website. • Collection: MHRA guidance on coronavirus (COVID-19) • MHRA regulatory flexibilities resulting from coronavirus (COVID-19)		Positive benefit/risk profile and completed efficacy, quality, and safety data required	Yes. Specific conditions are usually attached to the R174 temporary authorisation to ensure the efficacy, safety and quality of the product. Specific conditions vary per product. Conditions requiring the submittal of further, longer-term clinical trial data can also be applied to the R174 temporary authorisation, as well as those related to pharmacovigilance and deployment.	Yes - completion of ongoing clinical trials and studies are required ahead of the issuance of a full Market Authorisation for the product.	Yes. Coronavirus Yellow Card reporting system, alongside normal Yellow Card reporting system	Yes. The National Institute for Biological Standards and Control, part of the agency, has been and will continue doing, independent laboratory testing so that every batch of the vaccine meets the expected standards of safety and quality.		EMA - reliance procedure (automatic recognition)	Yes. Vaccine Damage Payments Act 1979	The Act provides for payments to be made out of public funds.
USA	FDA	Yes, pursuant to Section 564 of the FD&C Act (21 U.S.C. 360bbb-3)	Emergency Use Authorization	Includes drugs and biological products and devices (processes in column L may differ between drugs and devices)	The EUA authority permits FDA to authorize unapproved products and unapproved uses of approved products as medical countermeasures to prepare for and respond to emergencies involving threat agents.		EUA standards are not the same standards as those for approval of a New Drug Application or Biological Licensing Application for marketing. Separate and distinct from use of a product under an investigational application such as an Investigational New Drug application (IND).	Yes. Based on the totality of scientific information available, including data from adequate and well-controlled trials if available, it is reasonable to believe that the product "may be effective" to prevent, diagnose, or treat serious or life-threatening diseases or conditions caused by the threat agent.			Yes. FDA committed to a transparent authorization process: For drugs and biologics, the following are posted to the web: EUA authorization, and if applicable Revocation letters Health care provider and patient fact sheets EUA Scientific review memos, subject to applicable disclosure laws In addition, during COVID FDA, for vaccine EUAs, Public advisory committee meetings materials		Yes. Criteria for Issuance includes: 1. Agent referred to in the Secretary's declaration can cause a serious or life-threatening disease or condition. 2. Based on the totality of scientific information available, including data from adequate and well controlled trials if available, it is reasonable to believe that the product "may be effective" to prevent, diagnose, or treat serious or life-threatening diseases or conditions caused by the threat agent. 3. Known and potential benefits of the product, when used to diagnose, prevent, or treat the disease or condition, outweigh the known and potential risks of the product.							
USA	FDA	Yes, pursuant to Section 564 of the FD&C Act (21 U.S.C. 360bbb-3)	Emergency Use Authorization	Includes drugs and biological products	The policy for EUA for Vaccines to Prevent COVID-19 is in effect for the duration of the pandemic. Note: issuance of an EUA for a COVID-19 vaccine is not based on the PHE declaration and may remain in effect beyond the duration of the PHE declaration if all other statutory conditions are met.		Investigational vaccines (Biologics) to prevent COVID-19 are assessed on a case-by-case basis based on target population, characteristics of the product, preclinical and human clinical study data on the product, and the totality of available scientific evidence relevant to the product.	Yes. Issuance of an EUA would require a determination by FDA that the vaccine's benefits outweigh its risks based on data from at least one well-designed Phase 3 clinical trial that clearly demonstrates the vaccine's safety and efficacy in addition to adequate manufacturing information to ensure its quality and consistency. Requested S/E/Q data is described in guidance.	Yes. Rolling submission.	Yes. Sponsors considering submission of an EUA request for an investigational COVID-19 vaccine should contact the FDA as early in the development as possible to discuss expectations and considerations for the sponsor's particular vaccine. FDA also recommends early communication on facility issues.	Yes. FDA committed to a transparent authorization process: - Briefing documents to be posted on the web - Public advisory committee meetings being livestreamed - EUA review memo posted on the web - FDA will brief interested parties and answer questions		Standard used for EUA: product "may be effective" and its "known and potential benefits outweigh the known and potential risks". EUA may be appropriate once studies have demonstrated the safety and effectiveness of the vaccine but before manufacturer has submitted and/or FDA has completed its formal review of the biologics license application. EUA application evaulation includes public advisory committee.		Yes. (TBC) EUA request should include strategies to ensure that ongoing placebo control clinical trials of the vaccine are able to assess longterm safety and efficacy (including evaluating for vaccine-associated ERD as well as decreased effectiveness as immunity wanes over time) in sufficient numbers of subjects to support vaccine licensure.	Yes. FDA expects that there would be an adequate plan for safety data collection among individuals vaccinated under an EUA. FDA recommends early planning of pharmacovigilance activities to facilitate post-authorization safety evaluations. FDA may require postmarketing studies or trials to assess known or potential serious risks.			No.	Yes. COVID-19 vaccines are covered under the Countermeasures Injury Compensation Program (CICP).	
Global	WHO	No. Established as a service to Member States and international procurement agencies, originally in response to the 2014-16 Ebola outbreak.	Emergency use listing	Vaccines, therapeutics and IVDs	Generally 12 months. When deemed necessary, EUL can be extended.	All decisions are reassessed at 12 months intervals or sooner if further data become available that could alter the original decision. Products may be taken off the EUL list earlier, if new data become available that change the benefit-risk balance of the product or immediately upon termination of the PHE.	Criteria for EUL: - disease for which the product intended is serious or immediately life threatening and has the potential of causing an outbreak, epidemic or pandemic; - existing products not successful in eradicating the disease or preventing outbreaks (in the case of vaccines and medicines); - product is manufactured in compliance with cGMP (medicines and vaccines) and under a functional QMS (IVDs); - applicant undertakes to complete the development of the product and apply for WHO prequalification. Additional criteria set for products intended for C-19. For vaccines, product has undergone phase IIb or III studies and manufacturer expects approval by 'NRA of record' within 6 months.	Yes. Submitted data should demonstrate a reasonable likelihood that the quality, safety and effectiveness/ performance of the product are acceptable and that the benefits outweigh the foreseeable risks and uncertainties in the context of a PHEIC.	Yes. Rolling submission for review of COVID-19 vaccines.	Yes. Early and ongoing consulation with WHO strongly encouraged. Presubmission meeting mandatory to discuss assessment pathway and plan for the submission of data.	Yes. In addition to normal measures (public assessment reports), WHO has: - developed dedicated webpages on COVID-19 product requirements, procedures and evaluation status/outcomes (including negative decisions); developed product roadmaps for the assessment, authorization and monitoring of vaccines to optimize intercations with manufacturers and NRAs; - organized regional webinars with NRAs to discuss the basis for issuing specific vaccine EULs; - shared product dossiers and WHO reports with NRAs through a secure electronic platform.		(1) application meets EUL requirements in demonstrating likelihood of benefits outweighing foreseeable risks; (2) authorization by NRA of reference; (3) commitment to conditions set in EUL for post-authorization monitoring.	No. However, noncompliance with the conditions for issuing an EUL may result in the withdrawal of the listing and consequent actions by NRAs in countries.	Yes. It is expected that the manufacturer will complete the development of the product for NRA licensure and WHO prequalification.	Yes. Obligations for vaccine manufacturers defined in approved RMP (PVP and risk minimization measures), with special consideration to monitoring and studies in LMICs. Obligations to report to PQ and NRAs. Collaborative models with manufacturers have also been developed to promote the passive/ active safety surveillance of COVID-19 vaccines across LMICs.	Yes, per PQ requirements in addition to independent lot release for each batch of prequalified or EUL'ed vaccine by the NRA of record. WHO has developed an operational tool (guidance) to expedite the batch release of COVID-19 vaccines by importing countries.		Yes. PQ relies whenever possible on the safety, efficacy and quality evaluations of other internationally recognized regulatory authorities and agencies ("WHO Listed Authorities"), focusing its efforts on programmatic considerations aimed at ensuring the suitability of products and its use in LMICs. Abridged pathways are described in PQ procedures on WHO website. Assessment pathway confirmed in pre-submission meeting. WHO participates in EMA'S OPEN pilot and participates in C-19 related discussions under ICMRA and other regulatory fora. See Narrative Summary for mechanisms established to expedite country authorizations.	WHO contributed to the design and set-up of the COVAX No fault Compensation (NFC) Program to support individuals suffering SAEs in AMC (Advance Market Access) countries that have received authorized (unlicensed) vaccines supplied under COVAX Facility until 30 June 2022. Independent third party administrator processes claims under the Program.	Lump-sum compensation in full and final settlement of claims by administrator. Financing through per dose levy charged for vaccines supplied through COVAX.

Deep dive report on the review of provisions and procedures for emergency authorization of medical products for COVID-19 among ICMRA members - July 2021

APPENDIX 3: Deep dive narrative summary of provisions and procedures for emergency authorisation of medical products for COVID-19 among ICMRA members – July 2021

Disclaimer: This narrative summary is meant to inform discussion amongst ICMRA authorities and authorities of other WHO members states on regulatory flexibilities/agilities in the context of COVID-19, other pandemics/emergency situations and routine regulatory conditions. It is not meant to infer WHO or ICMRA endorsement of the examples described herein, including those described in appendices.

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Part A - Facts

Canada (temporary emergency authorization transitioning to notice of compliance)

Canada's Interim Order Respecting the Importation, Sale and Advertising of Drugs for Use in Relation to COVID-19 took effect on September 16, 2020. This interim order, known as the ISAD IO, provided a mechanism to issue temporary emergency authorizations for COVID-19 drugs and vaccines to address the pandemic. The ISAD IO introduced temporary regulatory tools to expedite the authorization and licensing for importing, selling and advertising COVID-19-related drugs and vaccines without compromising standards for patient safety. The ISAD IO expired on September 16, 2021. The termination of the ISAD IO would have meant that drugs authorized through the interim order would no longer be legally permitted to be sold in Canada. As well, any drug establishment licence (DEL) issued through the interim order would be automatically cancelled. To ensure that COVID-19-related drugs and vaccines authorized under ISAD IO continue to be imported and sold in Canada, Health Canada introduced transition measures (Regulations Amending the Food and Drug Regulations (Interim Order Respecting the Importation, Sale and Advertising of Drugs for Use in Relation to COVID-19): SOR/2021-45). The review, authorization and oversight of COVID-19 drugs, including new drugs, can now be conducted under Canada's *Food and Drug Regulations* (FDR).

The Interim Order was designed to provide an expedited and agile temporary market authorization pathway for COVID-19 drugs, needed to address the urgent public health crisis. It supports the intent that intellectual property considerations should not delay Canadians' access to COVID-19 treatments for the purpose of responding to the COVID-19 public health crisis.

As a consequence of the review, authorization and oversight of COVID-19 drugs under the Regulations, manufacturers may benefit from intellectual property protections that are available in respect of a submission that results in an NOC.

Eligibility Criteria: a COVID-19 drug is defined in the Interim Order as a drug that is manufactured, sold or represented for use in relation to COVID-19. This includes:

- prescription and non-prescription professional use pharmaceuticals
- radiopharmaceuticals
- biologically-derived products such as vaccines, blood derived products, and products produced through biotechnology
- veterinary drugs

The scope and application of amendments to the *Food and Drug Regulations* to ensure that COVID-19-related drugs may continue to be imported and sold in Canada include:

- drug products authorized under the interim order
- manufacturers planning to file a submission for a Notice of Compliance (NOC) for a designated COVID-19 drug as defined in C.08.001.2

- establishments seeking a DEL related to COVID-19 drugs
- pre-positioning mechanism introduced under the ISAD IO to allow for the placement of COVID-19 drugs in Canadian facilities prior to the authorization to sell in Canada.

Submission, evaluation and approval requirements: The Interim Order allows the Minister of Health to account for urgent public health needs relating to COVID-19 in deciding whether to authorize a COVID-19 drug or establishment licence holder based on the provided evidence of safety, efficacy, and quality.

Under the amendments to the *Food and Drug Regulations*, for Health Canada to issue a Notice of Compliance (C.08.004) for the sale of a COVID-19 drug, the New Drug Submission (NDS) must meet the requirements of section C.08.002. For drugs relying on the modified requirements in C.08.002 (2.1), the NDS must contain enough evidence to support the conclusion that the drug's benefits outweigh the risks when used as indicated. The evidence takes into consideration the uncertainties around the drug in the context of the public health need related to COVID-19.

The *Food and Drug Regulations* were amended to allow manufacturers who seek approval for a COVID-19 drug to file a submission with an alternative data package where justified based on the urgent public health needs resulting from COVID-19. As more products emerge to address the public health needs brought upon by COVID-19, manufacturers should discuss data requirements with Health Canada prior to filing. This is balanced with the new authority to apply terms and conditions requiring the manufacturer to address risks and uncertainties after authorization.

The Guidance for market authorization requirements for COVID-19 vaccines was adopted on November 20th 2020 to provide additional guidance on COVID-19 vaccine criteria under the Interim Order. It was revised March 30, 2021 to provide guidance on developing the evidence and documentation needed to obtain an authorization and licensing for importing or selling a COVID-19 vaccine in Canada.

To file an application for a rolling review, sponsors should have at a minimum:

- non-clinical and clinical Phase II data that demonstrate promising evidence of safety and efficacy
- confirmation that Phase III trials have started and there are enough people enrolled to provide evidence of safety and efficacy within a reasonable amount of time (expected to be within 6 months from initial filing)
- evidence that manufacturing is in compliance with good manufacturing practices (GMP) and that product quality and consistency are well controlled.

Sponsors must also file a plan giving the anticipated timelines for submitting the various components of the application. A plan must be included in the initial filing.

Reliance provisions and approaches: The ISAD IO provides for the authorization of a drug based on certain elements being authorized by a foreign regulatory authority, this provision was not used and, as such, has not been introduced into the *Food and Drug Regulations*.

Collaborative review with international regulatory partners is possible in cases where manufacturers file a rolling submission simultaneously with Health Canada and another jurisdiction with which there is a mutual collaborative agreement (see also under Switzerland for a description of application review within the framework of the work-sharing initiative of the Access Consortium). Health Canada is also participating in the pilot phase of the European Medicines Agency's (EMA) "Opening our Procedures at EMA to Non-EU authorities (OPEN)" project.

Health Canada's lot release program allows the application of a risk-based approach which considers evidence on manufacturing quality and controls as well as testing from other international regulatory authorities (including the European Official Medicines Control Laboratory (OMCL) network).

Post-authorization commitments/requirements: Post-authorization regulatory obligations are determined on a case-by-case basis as set out through terms and conditions imposed on a COVID-19 drug authorization holder or establishment licence holder, including the continued accumulation of data on quality, safety and effectiveness. The Minister of Health may impose or amend a term or condition on the authorization at any time during the life of the authorization.

Companies are required to maintain records and file a risk management plan that includes a Canadian addendum compliant with Canadian regulatory requirements. The addendum is to include safety specifications, pharmacovigilance plan (PV) and risk minimization plan. Health Canada is sharing the risk minimization plan online as a component of its transparency measures. The PV plan may include activities additional to spontaneous reporting and requires monthly safety summary reports. COVID-19 drugs under the ISAD IO are subject to the post-market reporting requirements in the *Food and Drug Regulations*.

Validity: A temporary emergency authorization issued under the Interim Order is valid until the Interim Order expires on September 16, 2021. The amendments to the *Food and Drug Regulations* provide that an ISAD IO authorization will be revoked unless a submission is filed within:

- 90 days following the coming into force of the amendments, if the drug was authorized under the ISAD IO before the amendments came into force or
- 90 days following the issuance of an authorization under the ISAD IO, if the drug was authorized after the amendments came into force.

Where a submission has been filed within these timelines, the COVID-19 drug may continue to be sold under the ISAD IO authorization until the submission has been approved, rejected or withdrawn.

Subsequent entry drug applicants are not able to transition under the FDR. This is the case even after the ISAD IO ceases to have effect.

If a manufacturer fails to file a submission under the *Regulations* within the prescribed timelines, the manufacturer will have to wait until the product is authorized under the *Regulations* to resume sale.

Enhanced transparency measures: Transparency has been foundational throughout the pandemic. In addition to new transparency initiatives, existing activities were expanded and expedited. Examples of initiatives include:

1. Publication of new applications and new approvals (same day)
2. Creation of a "Regulatory Portal" that consolidates all pre- and post- market regulatory documentation. Examples of documents include: Product Monograph, consumer information, terms and conditions, all risk communications.
3. Creation of "Product Pages" for new treatments and vaccines. These pages explained the decision, post-market monitoring and provided links to all the regulatory information
4. Expedited posting of regulatory decision summaries (same day), scientific summaries of the review (within a week for vaccines) and clinical data packages.
5. Increased communication regarding post-market safety information. These included departmental statements, expedited safety reviews, and a web page dedicated to tracking adverse events.

Availability of the Risk Management Plan (upon request)

Injury compensation program:
All current and future Health Canada authorized vaccines or immunoglobulins that provide protection from preventable infectious disease, administered in Canada on or after December 8, 2020, will be covered under the VISP (Vaccine Injury Support Program). This includes vaccines authorized under the Food and Drug Regulations as well as the *Interim Order Respecting the Importation, Sale and Advertising of Drugs for Use in Relation to COVID-19*.

The VISP is being administered and delivered independently by RCGT, with funding from the Public Health Agency of Canada. Decisions on individual claims are made by a committee of independent medical experts and neither the Public Health Agency of Canada or Health Canada is involved in the decision of individual claims.[1]

The Government of Québec introduced the Vaccine Injury Compensation Program in 1985. Québec's Minister of Health and Social Services has entered into an agreement with the Société de l'assurance automobile du Québec (SAAQ) whereby the SAAQ calculates and pays the compensation to cases who obtain favourable decisions. Amounts are calculated pursuant to the rules and regulations prescribed in the Automobile Insurance Act and are identical to those awarded in case of an automobile accident.[2]

Canada first created the Interim order respecting the importation and sale of medical devices for use in relation to COVID-19 on March 18, 2020. This Interim Order was replaced by a second Interim Order on March 18, 2021 to extend the flexibilities of the first, so that devices can continue to be sold and imported in Canada. The Interim Order introduced an expedited pathway to authorize medical devices related to COVID-19 in order to provide faster access to these devices in Canada without compromising safety or effectiveness. Prior to the end of the second Interim Order, Health Canada will introduce Transition Regulations for two years in order to regulate the devices authorized under the Interim Order and allow sale to continue.

Eligibility Criteria: All 4 classes of medical devices are eligible, provided that they can identify their direct use for COVID-19 and are required as a matter of urgent public health need. Expanded use authorizations are being given for new indications for devices already marketed in Canada.

Submission, evaluation and approval requirements: The Interim Order allows the Minister of Health to account for urgent public health needs relating to COVID-19 in deciding whether to authorize a medical device related to COVID-19, based on the evidence of safety, effectiveness and quality provided by the manufacturers. Under the Interim Order there is a flexible bar for safety and effectiveness criteria when compared to standard Medical Device Regulations requirements. There is no requirement for a Medical Device Single Audit Program Quality Systems Certificate. The pathway under the Interim Order for a Class I device authorization does not exist under the *Medical Devices Regulations*. Health Canada created the Guidance Document: Applications for medical devices under the Interim Order for use in relation to COVID-19, along with several other specific guidance documents for certain device types. The guidance document was updated when Interim Order No. 2 came into effect. The application and approval requirements vary by type of medical device.

Validity: The interim authorizations are in effect for a period of one year, or up to March 1, 2022 at the latest. Prior to the end of Interim Order No. 2, Health Canada plans to introduce Transition Regulations which will allow manufacturers to continue selling the medical device in Canada for two years, while giving them an opportunity to apply for a regular medical device licence or Medical Device Establishment Licence (MDEL) under the *Medical Devices Regulations*. The Transition Regulations are expected to be in place for two years. If a manufacturer has not received a medical device licence or MDEL under the *Medical Devices Regulations* by the end of the Transition Regulations, the device can no longer be sold in Canada.

China (conditional marketing authorization)

China's National Medical Products Administration (NMPA) has granted a conditional marketing authorization for a COVID-19 vaccine through a rolling submission.

Eligibility Criteria: Medicines, vaccines, medical devices/in vitro diagnostics. Eligibility criteria include the following:

1. Drugs that are used to treat serious and life-threatening diseases and for which no effective treatment(s) is available, and drugs urgently needed for public health, and whose clinical trials have already shown their efficacy and whose clinical value can be predicted.
2. Vaccines that are urgently needed in response to major public health emergencies or other vaccines that are identified as being urgently needed by the National Health Commission, whose benefits are evaluated to outweigh risks.

Submission, evaluation and approval requirements: Clinical data show that the benefits outweigh the risks, one of the following conditions shall be met:

1. Compared with the existing treatment(s), it can obviously improve the outcome of the disease.
2. Obvious efficacy can be obtained when the existing treatment(s) is intolerance or ineffective for patients.
3. It can be effectively combined with other key drugs or treatment(s) that cannot be combined with existing treatment(s) and have obvious efficacy.
4. The efficacy is equivalent to the existing treatment(s), but the compliance of patients can be significantly improved by avoiding serious adverse reactions to existing treatment(s) or significantly reducing harmful drug interactions.
5. It can be used to respond to newly occurred or expected needs for public health.

The Technical Guidelines for Conditional Approval and Marketing of Drugs released by the Center for Drug Evaluation of the State Drug Administration on November 19, 2020[3] defines the criteria and high level requirements for issuing a conditional marketing approval, including types of evidence that could be predictive of clinical value such as surrogate endpoints, intermediate clinical endpoints or early clinical trial data (for example, interim Phase 3 data for vaccines).

Post-authorization commitments/requirements: After obtaining the conditional approval for marketing, the drug marketing authorization holder must carry out new or ongoing clinical trials in accordance with the specific conditions attached to the drug registration certificate. These clinical trials are usually based on confirming the expected clinical benefits. The applicant should discuss and reach consensus with the drug review center on the research to be completed, the content of which should include at least the following: post-marketing clinical research plan, study completion date, final clinical research report submission date, and post-marketing risk management plan. The clinical study plan shall include the overall clinical trial plan and all clinical trial protocols proposed by the applicant and reviewed and accepted by the Center for Drug Evaluation (CDE).

The MAH shall take corresponding risk management actions for existing or identified risks and potential risks based on the established post-marketing risk management plan.

Validity: Validity is case-by-case and depends on the duration required to complete the post approval commitments.

Injury compensation program: "In 2005, China introduced an administrative no-fault one-time compensation scheme for adverse events following immunization (AEFI). The scheme aims to ensure fair compensation for those injured by adverse reactions following immunization."[4]

"In 2014, the programme in the People's Republic of China was amended requiring all 31 provinces to implement compensation mechanisms for vaccine injuries [4]. Administration of the Chinese programme involves all levels of government: filing of claims and causality assessment of events is done at district or county level; operational procedures for compensation are set at province level and general vaccine injury compensation policies including definitions of what constitutes a vaccine injury are determined at the central government level."[5]

> The Law [PRC Law on Vaccine Administration] establishes a compensation system for abnormal reactions to vaccination. A recipient of an immunization program vaccine who dies or suffers significant disability or organ and tissue damage is to be paid from the vaccination funds of the provincial level government if the damage falls within the scope of abnormal reactions associated with a vaccine or cannot be prevented (art. 56).[6]

Colombia (marketing authorization, emergency use authorisation, import authorisations)

Colombia's Ministry of Health and Social Protection through Decree 1787 of 2020 on 29 December 2020 provided the ability to process and grant a Sanitary Authorization for Emergency Use (ASUE, Spanish acronym) of drugs for the diagnosis, prevention and treatment of COVID-19 that still do not have the information required to obtain a marketing authorization. The Colombian regulatory framework contemplates alternatives for the importation and manufacture of medicines required during a health emergency, through a sanitary registration (Decree 1782 of 2014, marketing authorization), emergency use authorization (Decree 1787 of 2020, conditional authorization), import authorizations (others).

Eligibility Criteria: The eligibility criteria differ depending on the requirements that are met for the drug.

For a Marketing Authorization, the Sanitary Registration (Decree 1782 of 2014, Decree 2106 of 2019 - article 94, Resolution 1606 of 2014, Decree 1148 of 2020) applies to drugs that have culminated the research process and meet all the requirements for a marketing authorization.

For a Sanitary Authorization for Emergency Use (ASUE), the sanitary conditions are established through the *Decree 1787 of 2020* for the processing and granting of the ASUE. This applies to drugs that are in the last phase of research with preliminary results.

There are a number of Import Authorization options that apply to drugs that have been evaluated by WHO/PAHO or reference authorities:

i. Decree 822 of 2003, Article 1- Importation by declaration of Emergency: INVIMA may authorize, exceptionally, the importation of products without having obtained the sanitary registration, for example: When there are circumstances of sanitary emergency declared by the Ministry of Health or circumstances of force majeure or fortuitous event.
ii. Decree 249 of 2013: Importation through PAHO. For the importation of medicines and critical inputs in public health, made by public entities through the Pan American Health Organization - PAHO, the document issued by said Organization must be attached, which certifies that the products comply with the quality criteria defined by the World Health Organization. The labels, packaging and inserts of the products referred to in this decree shall be accepted as they come from the country of origin.
iii. Applies to drugs and medical devices that are not in the research stage and that have the approval of a health authority.
iv. Decree 481 of 2004, Article 10: Authorization as Vital not available for several patients.
v. Decree 1148 of 2020, Articles 4 and 5: Authorization as Vital unavailable for several patients during the duration of the health emergency.
vi. Decree 218 of 2019: Through donations for social and humanitarian purposes.
vii. Decree 4725 of 2005 – Article 45 or 48: Authorization for emergency use.
viii. Decree 1148 of 2020: Whereby sanitary requirements are established to facilitate the manufacture and importation of products and services to address the COVID-19 pandemic and other provisions are issued.

Submission, evaluation and approval requirements: The National Institute for Food and Drug Surveillance (INVIMA) offers the opportunity for an early dialogue prior to filing an application for an ASUE. The objectives of these meetings with respect to the pending filing of an ASUE for a COVID-19 drug are to

- guide, plan and optimize the study of the procedure to improve the capacity for review
- facilitate technical and scientific interaction and communication
- clarify procedural and documentary aspects that may guide a potential request
- allow INVIMA to know a preliminary scheme of quality, efficacy and safety of the drug
- verify progress status of development milestones and available information for the drug
- propose conditions for the progressive delivery of information and new evidence to be generated, as the development of the product progresses and the information of the dossier is completed.

The information shared during these early discussions is treated as confidential and will not compromise INVIMA's review of the COVID-19 drug.

The submission of an application for an ASUE must be submitted to INVIMA in CTD format and contain at a minimum Module 1 administrative information, Module 2 summaries of common technical documents, and according to the drug, the information in article 7 of Decree 1787:

7.2 Specific information
7.2.1 Chemical Synthesis Drugs
7.2.1.1. General quality data: The guidelines of the lCH guide will be taken into account M4Q.
7.2.1.2. Provides pre-clinical and clinical data requirements
7.2.1.3. Product labeling
7.2.1.4. Risk Management Plan and Pharmacovigilance in the context of the health emergency
7.2.2. BIOLOGICAL DRUGS
7.2.2.1. General quality data: The guidelines of the ICH guide will be taken into account M4Q.
7.2.2.2. Pre-clinical and clinical data
7.2.2.3. Product labeling
7.2.2.4. Risk Management Plan (PGR) and Pharmacovigilance (FV)

The applicant may also submit information corresponding to modules 3, 4 and/or 5 if they are available.

The INVIMA has 10 business days during which to deny or approve the ASUE. If new information is received, then there is a new term of 10 business days to deny or approve the ASUE.

Reliance provisions and approaches: Reliance on recognized authorities and institutions may be full or partial:

- GMP certification: full dependence
- Issuance of Emergency Use Authorization: partial dependence, or full dependence with a concept from a reference authority or WHO.

Recognized regulatory authorities/agencies from 'High Health Surveillance OECD member countries':

Argentina, Brazil, Canada, Denmark, France, Germany, Japan, Netherlands, Norway, Sweden, Switzerland, United Kingdom, USA and the EMA.

INVIMA is an NRA of regional reference (ARNr) as recognized through a PAHO-led benchmarking process. ARNr decisions are taken into account by some authorities in the Americas region.

Post-authorization commitments/requirements: MAHs granted emergency use authorization under Article 4. Sanitary Authorization for Emergency Use (ASUE) are expected to complete ongoing studies

and those requested by INVIMA to confirm a favorable benefit-risk balance of the product and obtain a sanitary registration (marketing authorization) in accordance with the regulations in force. The MAH must also comply with the risk management plans and pharmacovigilance strategies approved by INVIMA.

Validity: An ASUE granted by INVIMA is valid for one (1) year, counted from the date of the execution of the administrative act. It may be renewed only once for the same term, with the presentation of the respective application, in the terms and conditions indicated in the Decree 1787 of 2020, and in accordance with the schedule presented by the applicant, and approved by INVIMA, who will monitor it. Article 10 provisions state that the application for renewal must be made no more than 30 days in advance of the expiration date to INVIMA.

Injury compensation program: Yes, in Colombia there is a program for compensation for injuries contemplated in Law 2064 of 2020, which details the form of compensation in accordance with the evaluation against the cause of the damage.

European Union (conditional marketing authorisation)

The **European Union** (EU) is using the European Medicines Agency's (EMA) conditional marketing authorisation to expedite the approval of safe and effective COVID-19 treatments and vaccines during the COVID-19 pandemic. The conditional marketing authorisation allows for the "approval of a medicine that addresses unmet medical needs of patients on the basis of less comprehensive data than normally required. The available data must indicate that the medicine's benefits outweigh its risks and the applicant should be in a position to provide the comprehensive clinical data in the future."[7]

> CMA is used in EU legislation for emergency situations in response to public health threats. This authorisation requires demonstration of a positive benefit-risk balance, allowing for additional post-marketing data to be provided on the condition that the company supplies these data as specific obligations within defined timelines. Specific obligations generally include clinical studies and exceptionally, in the context of emergencies, studies to provide further assurance on the pharmaceutical quality of the vaccines. The EMA's evaluation was expedited by making use of rolling reviews, specifically designed by the EMA, that allowed assessment of discrete datasets as soon as they became available.[8]

Eligibility Criteria: The medicine/vaccine is intended for treating, preventing or diagnosing seriously debilitating or life-threatening diseases.

Submission, evaluation and approval requirements: The EMA offers rapid procedures to accelerate the regulatory pathway "for initial marketing-authorisation applications for the treatment or prevention of COVID-19, as well as for applications to 'repurpose' medicines already authorised for other conditions,

by extending their indications to include COVID-19."[9] These include rolling review, accelerated assessment and conditional marketing authorisation.

Rolling review

The submission is provided to the EMA in eCTD format. The information in a rolling review includes the application form, Module 2 overview(s), as well as newly available data and responses to all questions from previous review cycles.

Accelerated assessment

A request must be made at least two to three months before submitting the marketing authorisation application. Note that the accelerated assessment reduces the review to 150 days but cannot be considered for medicines and vaccines that are undergoing a rolling review.

Conditional marketing authorisation

All of the following criteria must be met for the EMA's Committee for Medicinal Products for Human Use (CHMP) to grant a conditional marketing authorisation:

- the benefit-risk balance of the medicine is positive;
- it is likely that the applicant will be able to provide comprehensive data post-authorisation;
- the medicine fulfils an unmet medical need;
- the benefit of the medicine's immediate availability to patients is greater than the risk inherent in the fact that additional data are still required.[10]

There are conditions on a marketing authorisation that the marketing authorisation holder must fulfill within specific timelines, and these are published in the European public assessment report.

The EMA published on November 16, 2020 EMA considerations on COVID-19 vaccine approval to provide information about

- clinical requirements for marketing authorisation: *vaccine safety and efficacy will have been demonstrated in adults and should include individuals with pre-existing comorbidities and individuals aged above 65 years*
- clinical efficacy: *it is expected that at least one well-designed large-scale Phase 3 efficacy trial would be required to support the marketing authorisation of a COVID-19 vaccine.*
- clinical safety: *The evaluation of safety of SARS-CoV-2 vaccines will follow the standard principles outlined in EMA guidance documents.*
- post-approval follow-up for safety and efficacy: *Whenever feasible, the EMA has recommended that clinical trial participants should be followed for safety and efficacy within their randomised groups for at least one year after completing vaccination.*[11]

Reliance provisions and approaches: The EMA initiated the OPEN pilot in December 2020 to increase international collaboration on the evaluation of COVID-19 vaccines and therapeutics. The objective of the OPEN pilot project is to allow active international participation in the scientific evaluation of C-19 products where confidentiality arrangements are in place with non-EU regulatory authorities and selected international organizations (including WHO)—in line with the principle of reliance and global good regulatory practices. It is hoped that broader participation may accelerate development and assessment of C-19 products and bring in additional expertise and resources where needs and products are the same.

EMA also serves as the 'regulatory agency of record' for a number of WHO emergency use listed vaccines and as a reference agency for a number of regulatory authorities, as captured under individual country responses.

Post-authorisation commitments/requirements: Conditional marketing authorisation includes specific legally binding post-authorisation obligations. The EC/EMA have the authority to take regulatory actions, revoke conditional marketing authorisation in case of non-compliance and potentially levy fines.

Post-authorization obligations are established on a case-by-case basis as part of the conditional marketing authorization, but as a minimum would include:

- the completion of ongoing and planned studies to confirm the benefit-risk profile leading to a full marketing authorization
- post-authorization safety activities defined in the risk management plan, and core RMP for C-19 vaccines, including in the latter case monthly safety updates, enhanced passive surveillance, implementation of traceability measures (for all biologicals) and, as required, post-authorization safety studies
- standard manufacturing and batch testing requirements.

The following guidance documents provide detailed information on post-authorization safety obligations:

Pharmacovigilance Plan of the EU Regulatory Network for COVID-19 Vaccines

Consideration on core requirements for RMPs of COVID19 vaccines - coreRMP19 guidance

Validity: A conditional marketing authorisation is valid for one year and it is renewable.

Injury compensation program: There is no overall vaccine injury compensation program within the EU. With a Conditional Marketing authorisation the liability regime is the same as for other market authorisations. The market authorisation holder is responsible. Emergency use provides for only very limited exemption from liability for the company, while with compassionate use the liability is with the prescriber.

Germany (no conditional/temporary/emergency use authorisation is granted)

Germany, on 25 May 2020, issued an Ordinance assuring the supply of products for medical needs for the population in the context of the epidemic caused by the coronavirus SARS-CoV-2 (Supply Assurance for Medical Needs Ordinance - Medizinischer Bedarf Versorgungssicherstellungsverordnung - MedBVSV). The Ordinance includes products for medical needs to the population "during the epidemic situation **of national scope** that the German Bundestag recognised on 28 March 2020." Through the Ordinance, there are two ways in which medicinal products can be placed on the market for COVID-19:

1) Procurement and placing on the market by the Federal Ministry of Health itself. For these products, the MedBVSV provides for a series of exemptions from the provisions of the German Medicinal Products Act.
2) The NRA can grant an exemption from Section 21 (1) of the German Medicinal Product Act (Exemption from the obligation to obtain a marketing authorization) in individual cases.

Eligibility Criteria: Includes vaccines and biomedicines. All products for medical needs that are necessary for the supply of the population during the epidemic situation. Products for medical needs "are medicinal products, their active ingredients, source materials and excipients, narcotics in Annexes II and III of the Narcotics Act, medical devices, laboratory diagnostics, aids, items of personal protective equipment and products for disinfection."[12]

Submission, evaluation and approval requirements: After liaising with the Ministry of Health, the manufacturer submits to the National Regulatory Authority (NRA) documents relating to information on quality, efficacy and safety for evaluation. The NRA provides an opinion/assessment report. The supply and placing on the market by the Ministry of Health is only permitted if the quality of the medicinal product is guaranteed and a positive benefit/risk ratio can be expected for the prevention or treatment of the respective disease. Final delivery/administration to the end user must occur via physician or pharmacist.

The Ordinance offers an exemption from the obligation to obtain a marketing authorization, if necessary. This exemption can be granted by the NRA in individual cases, after a benefit-risk assessment has been carried out and if this exemption is necessary to ensure the supply of medicines to the population. There can be deviations from sections concerning:

- Section 3: The term 'substance' and Section 4: Definition of additional terms, including: Finished medicinal products; Blood preparations; Sera; Vaccines; Allergens; Test sera; Test antigens; Radiopharmaceuticals; Advanced therapy medicinal products; Manufacturing; Quality; Batch; Placing on the market; Requiring a marketing authorisation or registration; Active substances; Clinical trials; Risk; Risk-benefit balance; Risk Management Plan
- Section 11: Package leaflet

- Section 15: Expert knowledge
- Section 16: Limitation of the manufacturing authorisation
- Section 17: Deadlines for the granting of marketing authorisations
  Or
- Section 22: Marketing authorisation documents
- Section 23: Particular documents required for medicinal products intended for administration to animals
- Section 24: Expert opinions
- Section 25: Decision on marketing authorisation
- Section 26: Guidelines for the testing of medicinal products

Under the Ordinance, in individual cases:

- The NRA can order a deviation from labelling requirements, as pharmaceuticals may be placed on the market without a label and package insert.
- Products whose expiry date has expired may be placed on the market, if it is certain that the quality, effectiveness and safety of these drugs are not significantly impaired.
- Exceptions to Sections 72 import authorisation, Section 72a Certificates may be permitted if the NRA after carrying out a risk-benefit assessment determines that the exception is necessary to ensure the supply of the medicines and that the quality, efficacy and safety of the imported medicines are guaranteed.
- Exceptions may be allowed to Section 21(1) Obligation to obtain a marketing authorisation, (1) Finished medicinal products, Section 22 Marketing authorisation documents, Section 24, Expert opinions, Section 25, Decision on marketing authorisation and Section 26 (2), Guidelines for the testing of medicinal products, Section 28, Power to impose conditions, Section 29 Obligation to notify, renewal of the marketing authorisation and Section 32 Official batch testing.
- Exceptions to the deadlines provided for in Section Six of the Medicines Act on the basis of a risk-benefit assessment to be carried out by it, if this is to ensure that the population is supplied with medicinal products is required.

Reliance provisions and approaches: The evaluation the German NRA is obliged to perform, according to the MedBVSV, has to be a full evaluation of all available data. Assessment reports, certificates etc. from other NRAs can be used as supporting documentation.

Post-authorization commitments/requirements: Since no conditional/temporary/emergency use authorization is granted, the MedBVSV does not contain provisions for post-approval commitments/requirements. However, for the medicinal products without a marketing authorization that are distributed/placed on the market—based on the MedBVSV in accordance with the abovementioned criteria—all pharmacovigilance provisions of the German Medicinal Products Act apply without exception. Furthermore, the NRA usually performs batch testing for specific products, e.g. vaccines.

Validity: The applicability of the MedBVSV is limited in time. It ceases to be in effect when the German Bundestag declares the epidemic situation of national importance to be over. The temporary supply/placing on the market of medicinal products without market authorisation based on the MedBVSV is no longer possible as of the date the MedBVSV ceases to be effective.

Injury compensation program: "In 1961, Germany was the first country to implement a no-fault compensation programme that covered vaccine injuries."[13]

> Legislation pertaining specifically to compensation for vaccine injury is included in a larger statute that involves the control of infectious disease (the Federal Communicable Diseases Act). Many of the provisions in the legislation regarding administrative procedures are dictated by another statute, the Federal Social Assistance Law. The compensation program is administered by authorities in each Land, the political subdivisions in the Federal Republic of Germany.[14]

Japan (priority review, special approval for emergency)

Regarding the therapeutics, vaccines, medical devices and diagnostics to use against COVID-19 measures, the Ministry of Health, Labour and Welfare (MHLW) decided to grant those products authorization subject to the priority review under the Administrative notice on 13 April, 2020. And, in addition, MHLW is able to grant Special Approval for Emergency in Japan under article 14-3 of the *Pharmaceuticals and Medical Devices Act (PMD Act)*. On 2 September 2020, the PMDA published Guidelines "Principles for the Evaluation of Vaccines Against the Novel Coronavirus SARS-CoV-2" for vaccine evaluation.

Eligibility Criteria (Special Approval for Emergency)

Under article 14-3 of PMD Act, a certain medical product may be approved when

- An emergency situation requires an unapproved medical product to be used to prevent damage to the public health caused by the spread of diseases,
- Such emergency situation cannot be managed appropriately by any means other than the use of the unapproved product, and
- Such product is legally available in a country with a regulatory system for medical products that is equivalent to Japan.

Note: For medical products to be used against COVID-19 prior consultation is required.

Submission, evaluation and approval requirements:

In principle, submission requirements are the same as for general approval. MHLW/PMDA evaluate/investigate its application under the highest prioritization.

General considerations regarding nonclinical and clinical evaluations of investigational preventive vaccines for infectious diseases:

- Guidelines for Nonclinical Studies of Preventive Vaccines for Infectious Diseases (PFSB/ELD Notification No. 0527-1, dated May 27, 2010)
- Guidelines for Clinical Studies of Preventive Vaccines for Infectious Diseases (PFSB/ELD Notification No. 0527-5, dated May 27, 2010)

Given differences in benefit-risk judgement based on the situation of each country/region and ethnic factors that might affect the efficacy and safety of the SARS-CoV-2 vaccine there may be a need to conduct a clinical trial in Japan to evaluate the efficacy and safety of the vaccine in Japanese subjects.

"For principles concerning the quality of a SARS-CoV-2 vaccine, the ICH guidelines regarding the quality of drugs and biological medicines, and existing guidelines in Japan and overseas can be used, depending on the modality of the investigational SARS-CoV-2 vaccine"[15]

Plans for completion of post-approval activities.

When the product may be applied as Special Approval for Emergency, the application form and clinical data are necessary (the other data can be submitted afterwards).

Reliance provisions and approaches: Activation of the Special Approval for Emergency requires the product to be legally available in a country with a regulatory system for medical products that is equivalent to Japan through designation by the Cabinet Order for SAE. For COVID-19 related medicines, including vaccines and biologics, the following countries were designated: USA, UK, Canada, Germany, France.

Validity: Validity of Special Approval for Emergency is until the time when the Minister for Health, Labour and Welfare withdraws the approval in a case when the conditions of the eligibility criteria no longer persists or withdrawal is necessary to prevent damage to the public health.

Post-authorization commitments/requirements: Post approval requirements are the same as general approval. The surveillance plan is to be determined at the time of approval.

As stipulated in the "Principles for the Evaluation of Vaccines Against the Novel Coronavirus SARS-CoV-2," the marketing authorization holder must take appropriate post-marketing actions for safety based on the safety information obtained from the clinical studies. Following approval, the marketing authorization holder needs to organize a system that makes it possible to properly and rapidly collect the safety information in Japan and overseas and promptly provide it to all medical and other institutions concerned. This would include collecting safety information for general and/or specific groups (e.g. pregnant women, pediatric population).

Long-term follow-up results of large-scale clinical studies and new clinical trials must be reported by the manufacturer to PMDA and publicized.

Injury compensation program: There are two vaccine injury compensation programmes in Japan, one for the National Immunization Program (NIP) for sufferers from vaccines and one for the conventional compensation programme for therapeutics.

> The vaccine health damage relief system (a no-fault compensation scheme authorised by the Immunisation Act of 1976) is managed by the Japanese Ministry of Health, Labour and Welfare (MHLW) and prefectural governments. …
>
> Japan is unique in that it has a no-fault compensation scheme for drugs financed mainly by contribution from pharmaceutical companies. In Japan, the scheme for drugs was introduced in 1979 and is authorised by the Pharmaceuticals and Medical Devices Agency (PMDA).[16]

"The programme in Japan is also implemented at all levels of government."[17]

Republic of Korea (conditional market authorisation)

The **Republic of Korea** uses its existing *Regulation on approval and review of biological products*, MFDS Notification No.2021-29, Article 41 (Fast Track review, etc.) to regulate medicines (biologicals) and vaccines during a pandemic. Through a submission that qualifies for Fast Track Review, a conditional market authorisation may be issued by the Ministry of Food and Drug Safety (MFDS).

Eligibility Criteria: Article 41 (Fast Track Review, etc.) provides the regulatory authority for the Minister of MFDS to allow the submission of some documents required under this regulation after product approval or review to approve through the fast-track process preferentially. This includes

> 3. Pharmaceuticals that may have preventive or therapeutic effects against bioterrorism infectious disease and other pandemic.

Submission, evaluation and approval requirements: Article 41 allows the submission of some documents required after product approval and the review to approve through the fast track process preferentially.

A recent review by the MFDS for a domestic COVID-19 vaccine used a rolling submission prioritizing safety. The following data was reviewed and evaluated:

- non-clinical, clinical and quality data
- comparability of drug substance and drug products between the domestic COVID-19 vaccine was evaluated by testing and evaluating its comparability to that of the European countries

The MFDS used a 3-Tiered Advisory Review:

> 1) the "Advisory Committee for the Safety and Efficacy Assessment of COVID-19 Therapeutics/Vaccine,"
>
> 2) the "Central Pharmaceutical Advisory Committee" (legal advisory body of MFDS in accordance with the Pharmaceutical Affairs Act), and
>
> 3) the "Final Evaluation Committee" to obtain expertise and maintain objectivity in the market authorization evaluation process for COVID-19 vaccine.[18]

Post-authorization commitments/requirements:

Product specific conditions can be issued. Commitments include:

- the continued monitoring of safety and effectiveness
- the submission of results from ongoing studies
- safety monitoring and activities as defined in the RMP.

Validity: 5 years (can be renewed).

Injury compensation program: "The Korea National Vaccine Injury Compensation Program (KVICP), which was established in 1994, compensates individuals who experience certain AEFI for vaccines that are recommended by the government."[19]

Kingdom of Saudi Arabia (conditional approval)

The **Kingdom of Saudi Arabia** has pharmaceuticals and biological products intended for prevention or treatment of COVID-19 to be given a conditional approval.

Eligibility Criteria: Medicines and vaccines for the prevention or treatment of COVID-19

Submission, evaluation and approval requirements: The Saudi Food and Drug Authority (SFDA) is responsible for reviewing and granting approvals of medicines and vaccines. The following are required in a submission:

I. Regulatory

a. Complete file in eCTD format according to GCC Module 1 Specification Version 1.5
b. Cover letter
c. Application Form

II. Chemistry, Manufacturing, and Controls Requirements

a. Manufacturing.

b. Control of drug substance and drug product
c. Analysis

The conditional authorization request should include information on CMC; a list of each site where the product would be manufactured and supplied to Saudi Arabia, and relevant information about each site to demonstrate compliance with good manufacturing practices.

Each rolling package should include a tabulated summary of its contents and any updates should be clearly indicated, this will help to facilitate reviewing process.

If additional data is supposed to be submitted in a subsequent package, the expected submission date should be provided

III. Safety and Effectiveness Requirements

a. Non-clinical (Toxicology and Pharmacology)
b. Clinical efficacy
c. Clinical safety

IV. Risk management plan (RMP)

A risk management plan file in accordance with Saudi Good Pharmacovigilance Practice Guideline.

V. Product information:

a. **SPC (Summary of Product Characteristics)**: Add contact information of National Pharmacovigilance Center in accordance to GCC Guidance for Presenting SPC, PIL, and Labeling Information.
b. **PIL (Patient Information Leaflet)**: Submit Arabic and English versions of the PIL in accordance to GCC Guidance for Presenting SPC, PIL, and labeling information.

The sponsor may submit a rolling submission. The SFDA created a new regulatory guideline to register COVID-19 vaccines which allows the company to submit portions of the regulatory application to the SFDA as they are completed.

The SFDA will test and take samples from each received shipment to ensure their quality and safety before use. This follows the evaluation of safety, efficacy and quality data and obligations to meet international GMP standards.[20]

Reliance provisions and approaches: Not applicable in COVID-19 vaccine and treatment.

Post-authorization commitments/requirements: Given the intent to expedite the approval of a vaccine, the submitted requirements may not be as comprehensive as that of a typical drug submission. SFDA will ask for additional requirements (including samples) from the applicant or authorisation holder. The companies must provide further data from ongoing or new studies within pre-defined deadlines to confirm that the benefits continue to outweigh the risks.

Validity: A conditional approval is granted.

Singapore (interim authorisation)

Singapore's Health Sciences Authority (HSA) introduced the Pandemic Special Access Route (PSAR) "to facilitate early access to critical novel vaccines, medicines and medical devices during a pandemic, such as the current COVID-19 pandemic."[21]

Eligibility Criteria: For designated health products which the Government of Singapore requires during a pandemic.

Submission, evaluation and approval requirements: An interim authorisation under PSAR would be considered, if

i) there is reasonable quality, safety and efficacy (QSE) data suggesting that the potential benefits outweigh the known risks when used during the COVID-19 pandemic; and
ii) there is continuing QSE data generated from ongoing studies to support the eventual transition of the interim authorisation to full registration. Refer to link on Minimum Data Requirement for Approval via the Pandemic

The PSAR allows for data to submitted on a rolling basis. Initial data can be provided to begin the review process and then additional data is provided as on-going studies are completed. A rolling submission plan must be submitted that outlines the sequence and timelines for the subsequent data submissions.

> Although companies can start submitting data from the early development stages, HSA will only grant PSAR authorisation for the vaccine, medicine or medical device after the data accrued by the company has been assessed by HSA to demonstrate that it meets the required safety, efficacy and quality standards, and that the benefits outweigh the known risks. There should also be no significant adverse events, and relevant studies have to be submitted to HSA by the time the company applies for PSAR authorisation.[22]

The HSA has published HSA Proposed Minimum Data Requirement for Approval via the Pandemic Special Access Route [PSAR] for Supply of Emergency Therapeutic Products for

- Interim Authorisation of a COVID-19 Vaccine Under PSAR
- Interim Authorisation of a COVID-19 Therapeutic Monoclonal Antibody Under PSAR

The interim authorisation has a condition attached to it that the company must continue to submit "longer term follow up data to HSA to assure the continued effectiveness and safety of the vaccine."[23] The HSA can terminate the interim authorisation if the benefits no longer outweigh the risks.

Post-authorization commitments/requirements: Submission of quality, safety and efficacy data generated from ongoing studies as well as periodic reporting on real world safety and effectiveness to HSA (e.g. monitoring the impact of new mutations in viral genome on performance of COVID-19 tests).

Validity: Companies are required to file an application to transition the product from the PSAR interim authorisation to a full registration, once sufficient data is available.

Injury compensation program: "The Vaccine Injury Financial Assistance Programme for COVID-19 Vaccination (VIFAP) provides one-time goodwill financial assistance to persons who experience serious side effects that are assessed to be related to COVID-19 vaccines administered in Singapore."[24]

Switzerland (temporary authorization)

Switzerland, on 18 March 2016, approved the Temporary authorisation to use medicinal products in accordance with Article 9b para 1 TPA as a part of revision of the Therapeutic Products Act (TPA). "The Agency may, for a limited period of time, permit certain persons or a certain group of persons outside the scope of clinical trials to use medicinal products according to Article 9 paragraph 2 letter d."[25] Of note, Article 9b para 2. is one of the provisions upon which Switzerland's COVID-19 Ordinance 3 is based.

Eligibility Criteria: Swissmedic's Guidance document for Temporary authorisation for human medicinal products HMV4 provides details under 5.1.1 for the criteria. In brief these are:

a. The product is used "to identify, prevent or treat a disease that can lead to serious invalidity, severe suffering possibly resulting in death or to the death of a patient in the short term."
b. No alternative and equivalent medicinal product is authorised in Switzerland.
c. Major therapeutic benefit is expected from use of the product for which authorisation is being requested.
d. The applicant is expected to be able to supply the necessary data per section 2 of the TPLO before the temporary authorisation expires with a view to achieving ordinary authorisation.
e. It takes so long to compile all the required data and to process and evaluate the data under letter d in an ordinary authorisation procedure as per Art. 11 TPA that irreversible damage in patients would result or worsen or this would be associated with severe suffering.[26]

Submission, evaluation and approval requirements: Switzerland, on 19 June 2020 brought into force Ordinance 3 on Measures to Combat the Coronavirus (COVID-19). This Ordinance under Article 21

provides exceptions to the requirement of authorisation for medicinal products that are manufactured with active substances under Annex 5 for the treatment of COVID-19:

> Medicinal products that are manufactured with active substances under Annex 5 for the treatment of COVID-19 patients may, provided an application for authorisation of a medicinal product containing one of these active substances has been filed, be placed on the market without authorisation pending Swissmedic's decision on authorisation. When examining applications for authorisation, Swissmedic may permit a relaxation of the relevant requirements for such medicinal products under the law on therapeutic products on the basis of a risk-benefit analysis.[27]

Article 21 also provides that "Amendments to the authorisation for a medicinal product authorised in Switzerland containing an active substance under Annex 4 number 1 that is used to prevent and treat COVID-19 in Switzerland may be made immediately after filing a corresponding amendment application. Swissmedic may permit a relaxation of the relevant requirements for such amendments under the law on therapeutic products on the basis of a risk-benefit analysis."[28]

Article 22 additionally provides exceptions that allow the import of a medicinal product containing active substances listed in Annex 5 for the treatment of COVID-19 patients following the submission of an authorization application but prior to its approval.

In response to the COVID-19 pandemic, Swissmedic also published the Guidance document Authorisation procedures for Covid-19 medicinal products during a pandemic HMV4 on 18 September 2020. Swissmedic advises applicants to request a Scientific Advice meeting and then a Pre-submission Advice meeting. The applicant, during the Pre-submission Advice meeting, can request to submit the authorisation application as a rolling submission along with a plan for the submission of the data packages. "The applicant is required to inform Swissmedic in advance of the submission date for each individual data package so that it can plan the staff resources required to review the data material."[29]

Reliance provisions and approaches: If a medicinal product has already been authorised in a country with a comparable control system for medicinal products, Swissmedic, at the request of an applicant, will take into account the results of the assessment by the reference authority during the authorisation procedure based on Article 13 Medicinal products and procedures authorised in foreign countries, TPA. Reduced assessment under application of Art. 13 TPA is also possible for an application for temporary authorization if the product in question fulfils all the following conditions:

a) The medicinal product is intended to prevent a transmissible infectious disease that may cause severe harm or serious suffering with potentially fatal consequences.

b) The medicinal product's indication is identical to the indication approved by the reference authority.

Current list of countries with comparable human medicinal product control: Australia, Canada, EEA (European Economic Area) Member States (EU and European Free Trade Association countries), Japan, New Zealand, Singapore, United Kingdom, USA.[30]

It is also possible to ask for an authorisation application to be reviewed within the framework of the work-sharing initiative of the Access Consortium. The participating authorities coordinate the review of the corresponding applications, which must be submitted in at least two of the five possible countries. For the review of an application within the framework of the Access work-sharing initiative, all the authorisation documents and complete documentation needs to be submitted to Swissmedic.[31]

Post-authorization commitments/requirements: Applicants granted a temporary authorisation are expected to convert to an ordinary authorisation contingent on the fulfilment of the conditions imposed for the temporary authorisation. (See Validity below.)

Section 6.5.1 of the *Guidance document for Temporary authorisation for human medicinal products HMV4* advises applicants "The risk management plan (RMP) describes the risk aspects of the medicinal product, the planned pharmacovigilance activities and the risk-mitigation measures. The pharmacovigilance activities and the risk-mitigation measures cannot be planned or assessed definitively yet since knowledge of the risk aspects is still incomplete at the time the authorisation application is assessed. Specific conditions regarding safety specifications, the further collection of pharmacovigilance data and implementation of risk-mitigation measures may therefore be imposed."

Validity: Section 6.5.2 of the same guidance provides a timetable, conditions and ex officio extension for the temporary authorisation:

> The temporary authorisation is granted for a maximum of two years. The conversion to an ordinary authorisation is contingent on the fulfilment of the conditions imposed. All documentation on the fulfilment of conditions must be submitted to Swissmedic for review within two years of the official approval decision for the temporary authorisation, together with an application for the granting of ordinary authorisation.[32]

The temporary authorisation can be extended in scientifically justified exceptional cases if an application for extension is made at least 3 months prior to its expiry.

Section 6.5.4 describes how a temporary authorisation can be converted to an ordinary authorisation. When the authorisation provides documentation on the fulfillment of conditions, they must also submit an application to convert the temporary authorisation into an ordinary authorisation. The ordinary authorisation is valid for a period of five years, initially. The ordinary authorisation offers data protection.

Injury compensation program: "Since its establishment in 1970, the programme in Switzerland was administered at the cantonal level (each of 26 states that compose the confederation). In 2016, the

Swiss compensation policy was amended, and the administration of the programme is done by the central government."[33]

United Kingdom (temporary authorisation of the supply of unlicensed products)

The **United Kingdom**'s "preferred route to enable deployment of a new vaccine for COVID-19 is through the usual marketing authorisation routes."[34] The UK's Human Medicines Regulations 2012 contain article 174 that allows for the temporary authorisation of a medicinal product under pandemic conditions. Of note, prior to the UK's exit from the European Union, this implementing measure applied, "Regulation 174 is an implementing measure for Article 5(2) of the EU Medicines Directive 2001/83, representing the UK's choice of form and methods for doing so in 2012."[35]

On 25 March 2020, the UK's Coronavirus Act 2020 was enacted. It begins with an interpretation of the meaning of "coronavirus" and related terminology:

(1) In this Act—

> "coronavirus" means severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2);
>
> "coronavirus disease" means COVID-19 (the official designation of the disease which can be caused by coronavirus).[36]

On 16 October 2020, the UK's Human Medicines (Coronavirus and Influenza) (Amendment) Regulations 2020 (SI 2020/1125) *came into force. These regulations amend the Human Medicines Regulations 2012. The new regulation 174A was used to provide a temporary authorisation to Pfizer/BioNTech (BNT162b2), COVID-19 Vaccine AstraZeneca, and COVID-19 Vaccine Moderna for use in the UK. The COVID-19 Vaccine Moderna was then authorised* via the European Commission (EC) Decision Reliance Route (see Reliance provisions and approaches) *under a "'conditional approval' scheme. This means that further evidence on this medicinal product is awaited. New information on this medicinal product will be reviewed at least every year and this SmPC (Summary of Product Characteristics) will be updated as necessary."*[37] The COVID-19 Vaccine Vaxzevria (previously COVID-19 Vaccine AstraZeneca) was granted a national Conditional Marketing Authorisation from the MHRA with specific measures to be met within specified timelines. Of note, it is up to the company to decide whether they follow the reliance EC Decision Reliance Route and wait for the EMA decision first, or whether they apply directly to the MHRA for the national authorisation route (e.g. CMA). The company also has to apply to move from a Reg 174 approval to a CMA.

Eligibility Criteria: medicinal product, such as a COVID-19 vaccine.

Submission, evaluation and approval requirements: The Medicines and Healthcare products Regulatory Agency (MHRA) needs to be satisfied that there is sufficient evidence to demonstrate the safety, quality and efficacy of a vaccine before it will consider issuing a Regulation 174 temporary authorisation for the

supply of a vaccine. "A COVID-19 vaccine would only be authorised in this way if the UK's licensing authority was satisfied that there is sufficient evidence to demonstrate the safety, quality and efficacy of the vaccine."[38]

The requirements for a UK Regulation 174 emergency approval are very similar to the requirements for a conditional market authorisation. In both cases there needs to be sufficient data on quality, safety and efficacy to conclude that the risk/benefit analysis is positive.

An authorisation issued under Regulation 174 "is subject to a number of conditions attached under regulation 174A(1) to all the entities involved in the manufacture and supply of this product across the medicines supply chain."[39] These conditions can include general, quality, product information and instructions for use, non-clinical, clinical, pharmacovigilance, deployment, supply chain and distribution.

Reliance provisions and approaches: EMA - reliance procedure (automatic recognition).

The COVID-19 Vaccine Moderna was granted a Conditional Marketing Authorisation by the MHRA

> …via the European Commission (EC) Decision Reliance Route. This is when the marketing authorisation application made by the company references the decision made by the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP). The MHRA reviews this application, together with due consideration of the EC decision, before making an independent decision on the quality, safety, and effectiveness of the vaccine.[40]

Post-authorization commitments/requirements: Specific conditions are usually attached to the R174 temporary authorisation to ensure the efficacy, safety and quality of the product. These specific conditions vary per product and can range from specifying whom the product is suitable for (i.e. age group, whether the product can be used by pregnant/breastfeeding women, and those with underlying health conditions), setting batch testing and quality assurance standards*, and ensuring the appropriate storage is in place throughout the supply chain. Conditions requiring the submittal of further, longer-term clinical trial data can also be applied to the R174 temporary authorisation, as well as those related to pharmacoviglance and deployment.

* Additionally, independent batch release by the National Institute for Biological Standards and Control (NIBSC) will be performed on all batches to be supplied to the UK under authorization for temporary supply of COVID-19 vaccines under this Regulation 174A.[41]

Validity: A temporary authorisation is "valid until expressly withdrawn by MHRA or upon issue of a full market authorisation by the MHRA,"[42] while a conditional approval is reviewed at least every year.

Injury compensation program: The United Kingdom has the Vaccine Damage Payments Act 1979

> An Act to provide for payments to be made out of public funds in cases where severe disablement occurs as a result of vaccination against certain diseases or of contact with a person who has been vaccinated against any of those diseases; to make provision in connection with similar payments made before the passing of this Act; and for purposes connected therewith.[43]

United States (emergency use authorization)

Under section 564 of the Federal Food, Drug, and Cosmetic Act (FD&C Act), when the Secretary of the Department of Health and Human Services declares that an emergency use authorization is appropriate, FDA may authorize unapproved medical products or unapproved uses of approved medical products to be used in an emergency to diagnose, treat, or prevent serious or life-threatening diseases or conditions caused by chemical, biological, radiological, and nuclear (CBRN) threat agents when there are no adequate, approved, and available alternatives. These medical products, also referred to as "medical countermeasures" or "MCMs," include drugs (e.g., antivirals and antidotes), biological products (e.g., vaccines, blood products, and biological therapeutics), and devices (e.g., in vitro diagnostics and personal protective equipment). The Health and Human Services Secretary declared that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic, pursuant to section 564 of the FD&C Act, effective March 27, 2020.

FDA has issued guidance for sponsors and stakeholders on *Emergency Use Authorization of Medical Products and Related Authorities.* This guidance outlines the general requirements for submission of EUAs. In general, an EUA should include a well-organized summary of the available scientific evidence regarding the product's safety and effectiveness, risks (including an adverse event profile) and benefits, and any available, approved alternatives to the product. The exact type and amount of data needed to support an EUA may vary depending on the nature of the declared emergency or threat of emergency and the nature of the candidate product. FDA may seek additional data and information on a case-by-case basis to ensure that the statutory criteria for issuance of an EUA are met. The letter authorizing the emergency use may specify adverse event reporting, tracking of distribution, limits on promotion and other applicable conditions. The FDA has issued a number of EUAs for devices, drugs and biologics (for more information see Emergency Use Authorization | FDA).

EUAs for Vaccines

In addition to the EUA guidance, FDA issued a guidance entitled Emergency Use Authorization for Vaccines to Prevent COVID-19 Guidance for Industry on October 20, 2020 "to provide sponsors of requests for Emergency Use Authorization (EUA) for COVID-19 vaccines with recommendations regarding the data and information needed to support the issuance of an EUA"[44] The final guidance was issued on February 2021 and was updated on May 25, 2021 to include a new section that clarifies how the agency intends to prioritize review of EUA requests for the remainder of the COVID-19 public health emergency. The policy remains in effect only for the duration of the COVID-19 pandemic.

Eligibility Criteria: Investigational vaccines (Biologics) to prevent COVID-19 are assessed on a case-by-case basis considering the following criteria: target population, characteristics of the product, preclinical and human clinical study data on the product, and the totality of available scientific evidence relevant to the product.

Submission, evaluation and approval requirements: The submission requirements are the same as for general approval. However, the data set for the submission—other than those concerning test results of clinical studies—may be suspended (for a reasonable time).

> FDA acknowledges that an EUA for a COVID-19 vaccine may be requested to allow for the vaccine's rapid and widespread deployment for administration to millions of individuals, including healthy people, potentially following interim results from one or more clinical trials meeting pre-specified success criteria described in the analysis plan submitted to FDA. In this scenario, for a COVID-19 vaccine for which there is adequate manufacturing information to ensure its quality and consistency, issuance of an EUA would require a determination by FDA that the vaccine's benefits outweigh its risks based on data from at least one well-designed Phase 3 clinical trial that demonstrates the vaccine's safety and efficacy in a clear and compelling manner.[45]

Before issuing an EUA for a COVID-19 vaccine, the US FDA's Vaccines and Related Biological Products Advisory Committee (VRBPAC) has an open session "to discuss whether the available safety and effectiveness data support authorization of an EUA for the specific request under review."[46]

Post-authorization commitments/requirements: "It is FDA's expectation that, following submission of an EUA request and issuance of an EUA, a sponsor would continue to collect placebo-controlled data in any ongoing trials for as long as feasible and would also work towards submission of a Biologics License Application (BLA) as soon as possible. The ability of a sponsor to accrue this information about a COVID-19 vaccine is critical to ongoing assessment of its benefits and risks. FDA notes that there would need to be an adequate plan for safety data collection among individuals vaccinated under an EUA."[47]

Validity: The policy is in effect for the duration of the COVID-19 pandemic.

Since declaration of COVID-19 as public health emergency effective March 27, 2020, FDA issued EUA for 3 vaccines. The vaccines include: 1) BNT162b2 (Pfizer-BioNTech), granted on Dec 11, 2020; 2) mRNA-1273 (Moderna), granted Dec 18, 2020; and 3) Ad26.COV2.S (Janssen), granted Feb 27, 2021.

In addition to vaccines, FDA has issued EUAs for 10 drug and biological therapeutic products for the treatment of COVID-19 in adults and pediatric patients. The drugs include SARS-COV-1-targeting monoclonal antibodies, antiviral drugs, immune modulators, sedatives, renal replacement therapies.

Injury compensation program: COVID-19 vaccines are covered under the Countermeasures Injury Compensation Program (CICP). The CICP is funded through a Congressional appropriation to the U.S. Department of Health and Human Services.[48]

World Health Organization (emergency use listing)

Established in 1948, WHO has a unique global mandate as the specialized UN agency responsible for health, taking direction from and implementing actions set by the 194 Member States.

The WHO is not a regulatory authority as such, but rather supports regulatory authorities that oversee the authorization and surveillance of medical products through the development of international norms and standards, regulatory system strengthening, guidance, tools and platforms on the safe use of medical products and the fight against substandard and falsified products, and through the Prequalification programme. The goal is to promote affordable access to safe, effective and quality-assured medical products as an essential component of well-functioning health systems.

The Prequalification programme is a service provided by WHO to facilitate access to diagnostics, medicines, vaccines and immunization-related equipment and devices, and vector control products for high burden diseases meeting global standards of quality, safety and efficacy in order to optimize use of health resources and improve health outcomes. The prequalification process consists of dossier review, consistency testing or performance evaluation, site visits to manufacturers and CROs (contract research organizations), and post-listing surveillance based on international standards and best practices. This information, in conjunction with other procurement criteria, is used by the UN and other procurement agencies to make purchasing decisions. It also guides countries in the procurement of these products.

The Prequalification programme also serves to:

- build the capacity of regulatory authorities through the involvement of experts from NRAs in its activities, and
- promote regulatory efficiencies through support provided to joint regional inspection/assessment activities and mechanisms which facilitate product authorization at country level based on PQ (prequalification) listing and accompanying documentation.

In addition to invoking Emergency Use Listing (EUL) procedures described below, additional measures and innovations were introduced on a global scale to address product needs associated with the pandemic. These include:

- WHO Target Product Profiles (TPPs) for COVID-19 products[49]
- Development of guidance documents, tools and training materials to assist in the review and post-authorization monitoring of COVID-19 products
- A global model for carton and vial labelling for vaccines to be supplied under COVAX Facility[50]

- Roadmaps for the assessment of COVID-19 vaccines[51] [52] for EUL and/or prequalification which includes a global assessment model involving experts from NRAs across the WHO regions
- A secure electronic platform for NRAs to access product dossiers and assessment reports
- Real-time global COVID-19 vaccine safety monitoring and assessment mechanisms and committee
- Collaborative models with MAHs for promoting the passive and active safety surveillance of COVID-19 vaccines across LMICs.

Eligibility criteria: The WHO Emergency Use Listing Procedure (EUL) is a risk-based procedure for assessing and listing unlicensed vaccines, therapeutics and in vitro diagnostics with the ultimate aim of expediting the availability of these products to people affected by a public health emergency. While each of the product streams have specific requirements, the following common criteria must be met to be eligible for evaluation under the EUL procedure:

- The disease for which the product is intended is serious or immediately life threatening, has the potential of causing an outbreak, epidemic or pandemic and it is reasonable to consider the product for an EUL assessment, e.g., there are no licensed products for the indication or for a critical subpopulation (e.g., children);
- Existing products have not been successful in eradicating the disease or preventing outbreaks (in the case of vaccines and medicines);
- The product is manufactured in compliance with current Good Manufacturing Practices (GMP) in the case of medicines and vaccines and under a functional Quality Management System (QMS) in the case of IVDs; and
- The applicant undertakes to complete the development of the product (validation and verification of the product in the case of IVDs) and apply for WHO prequalification once the product is licensed.

Additional criteria for and prioritization of COVID-19 products may be found on the WHO website (see below). For vaccines, only those candidates that have undergone Phase 2b or Phase 3 studies and have been submitted to the NRA of record should be submitted for consideration. WHO may review rolling submissions, however, a decision on listing will not be made until the 'NRA of record' has approved/authorized the vaccine. (NRA of record is the NRA that first approved the vaccine and is responsible for the oversight of such vaccine.)

Submission, evaluation and approval requirements:

The EUL is a special procedure for unlicensed vaccines, medicines and in vitro diagnostics in the event of a Public Health Emergency (PHE) when the community/public health authorities may be willing to tolerate less certainty about the efficacy and safety of products given the morbidity and/or mortality of the disease and the lack or paucity of treatment, diagnosis/detection or prevention options. It is

intended to provide a time-limited listing for unlicensed products in an emergency context when limited data are available and the products are not yet ready for application for prequalification. As part of the EUL, it is expected that the manufacturer will complete the development of the product for licensure and WHO prequalification.

Submitted data should demonstrate a reasonable likelihood that the quality, safety and effectiveness/performance of the product are acceptable and that the benefits outweigh the foreseeable risks and uncertainties in the context of a PHEIC (public health emergency of international concern).

The EUL process involves an Expression of Interest for eligible products, pre-submission meeting, application, evaluation and listing decision. In order to expedite the overall review process of COVID-19 vaccines, WHO will review discrete data packages as they become available as rolling submissions in the CTD format. The pre-submission meeting serves to discuss the assessment procedure to be used (EUL or prequalification), assessment pathway, date of submission of the dossier, readiness of submission package and upcoming availability of supplemental data. Pre-submission meetings with potential applicants are mandatory.

A Product Evaluation Group (PEG) of experts is convened to conduct the technical review of safety, efficacy and quality data and make a recommendation on the benefit-risk balance of the product. A separate Technical Advisory Group (TAG) then provides WHO with a recommendation on whether an unlicensed medical product should be listed for emergency use, and if so, under what conditions.

Subject to the protection of commercially sensitive confidential information, WHO publishes the following information on the WHO website:

- the names of products and of manufacturers that have applied for EUL, the product code(s) submitted for EUL and the EUL status of each application;
- a WHO EUL public report summarizing the findings of the EUL assessment; and
- any negative outcomes of the EUL assessment.

In addition, WHO reserves the right to share full reports with the relevant authorities of any interested Member State and interested United Nations agencies. The status of COVID-19 products within the WHO EUL/PQ evaluation process—including those not meeting WHO requirements—are publicly available and are regularly updated on the WHO website.

Information on the essential data set and procedures for application, evaluation and post-authorization commitments/monitoring is provided in Annex 5 of the *Emergency Use Listing Procedure* (Version 13 December 2020) and supplementary guidance related to the product stream and COVID-19 on the WHO website including:

For vaccines:

- *Considerations for Evaluation of COVID-19 Vaccines* (Version 25 November 2020)

For diagnostics:

- *Invitation to manufacturers of in vitro diagnostics for SARS-CoV-2 to submit an application for Emergency Use Listing by WHO* (updated 26 May 2021)
- *Instructions and requirements for Emergency Use Listing (EUL) submission: in vitro diagnostics detecting SARS-CoV-2 nucleic acid and rapid diagnostics tests detecting SARS-CoV-2 antigens*
- *Instructions and requirements for Emergency Use Listing (EUL) submission: In vitro diagnostics detecting antibodies to SARS-CoV-2 virus*

Reliance provisions and approaches: Reliance and collaboration are guiding principles of the Prequalification (PQ) programme. PQ relies whenever possible on the safety, efficacy and quality evaluations of other internationally recognized regulatory authorities and agencies ('WHO Listed Authorities'), focusing its efforts on programmatic considerations aimed at ensuring the suitability of products, packaging, labelling and—for medicines and vaccines—pharmacovigilance plans and risk minimization measures in low- and middle-income country (LMIC) settings.

In order to accelerate vaccine authorizations at country level based on the EUL, regulatory roadmaps were developed that included agreements with the NRAs of record responsible for the emergency use authorization of the vaccine to discuss information, sharing of reports and other aspects of the evaluation; the involvement of subject matter experts from NRAs in different regions in the global assessment process; the sharing of product dossiers and WHO EUL reports (original listing and post-approval changes) with NRAs via a secure WHO electronic site with the consent of manufacturers, subject to signing a confidentiality agreement; mapping of regulatory requirements for emergency use of vaccines in the context of a PHE; and engagement with NRAs to promote use of the WHO EUL and address any bottlenecks. This global regulatory innovation also obviated the need to file applications in many LMICs.

The WHO has also established a risk-based mechanism similar to WHO Collaborative Registration Procedure (CRP) to expedite national decisions based on WHO EUL of COVID-19 IVDs. Similar to the principles established for CRP, the mechanism requires manufacturer's consent, signed confidentiality agreements, determination of product sameness, and an expectation to reach a national decision within 15 days of receipt of the WHO technical file and QMS review.

WHO also developed the *Operational Tool for efficient and effective lot release of SARS-CoV-2 (Covid-19) vaccines* to assist NRAs in applying the principles of reliance described in WHO Technical Guidelines to implement efficient and effective lot release of COVID-19 vaccines, including those granted WHO EUL.

As an example of reliance on PQ EUL or access to documents, 101 countries granted the necessary authorizations for the AstraZeneca and COVISHIELD vaccines within 15 days of the EUL. Furthermore, as

of 24 May 2021 a total of 88 countries had requested access to the secure WHO PQ site for between two to six vaccines listed for emergency use. WHO is also launching a facilitated procedure for accelerating national authorizations for COVID IVDs that have received EUL. NRAs are expected to come to a decision within 15 days of receipt of the technical product file and QMS review report.

WHO is participating in the EMA's OPEN pilot and collaborates in all ICMRA policy and working groups related to COVID-19, in addition to the vaccine cluster discussions and bilateral exchanges with regulatory authorities.

Post-authorization commitments/requirements:

Once a product has been listed under the EUL procedure, the development of the product must—whenever possible—continue to completion for marketing authorization with an NRA and be submitted to WHO for prequalification. Post-authorization requirements are defined as part of the EUL recommendations.

With respect to vaccines: Data from ongoing clinical trials, revised RMP as required, and passive and active surveillance data of the deployed vaccine must be submitted to WHO as the evaluation of these may have an impact on the risk-benefit assessment, thus on the listing status of the product. A report on the assessment of post-listing changes will be available for countries that have authorized the use of the listed vaccine. Guidance on the role and responsibilities of vaccine manufacturers for safety surveillance are also described in module 6.7 of the *Safety Surveillance Manual for COVID-19 Vaccines*.

With respect to IVDs: The manufacturer is required to ensure that activities are in place to monitor product safety, quality and performance post-EUL. It is expected that post-market surveillance activities will be in accordance with the WHO *Guidance for post-market surveillance and market surveillance of medical devices, including in vitro diagnostics*.

Validity: The validity of an emergency use listing in the context of a PHE is generally 12 months. All decisions to list a product in the EUL will be reassessed at 12 month intervals (or sooner, if further data become available that could alter the original decision). When deemed necessary, the emergency use listing can be extended. Products may be taken off the EUL list earlier, if new data become available that change the benefit-risk balance of the product or immediately upon termination of the PHE.

Injury compensation program: WHO contributed to the design and set up of the COVAX No-Fault Compensation Program. The Program, which became operational on 31 March 2021, provides no-fault lump-sum compensation in full and final settlement of any claims to individuals who have suffered a Serious Adverse Event resulting in permanent impairment or death associated with a COVID-19 vaccine procured or distributed through the COVAX Facility within any of the 92 AMC (Advance Market Commitment) eligible economy until 30 June 2022. The maximum period for submitting an application is 60 months (total of the 24-month period of vaccine administration + 36 months extended reporting period).

COVID-19 vaccines procured or distributed through the COVAX Facility are vaccines that have received regulatory approval or an emergency use authorization to confirm their safety, efficacy and quality. In practical terms, this means vaccines that have received a WHO EUL or, exceptionally, authorization by a 'stringent regulatory authority'.

The Program is administered by an independent claims administrator and financed through a per dose levy charged for vaccines supplied through COVAX. Donations to the COVAX Facility of COVAX distributed vaccines are covered by the Program provided they are for use in AMC eligible economies and the per dose levy is charged on the vaccine doses in question.

Details regarding the Program are available at www.covaxclaims.com.

Part B – Overall Analysis

Names and types of authorizations with validity conditions

Description

This is the overall analysis of names and types of authorizations with validity conditions based on data from Part A-Facts (columns C, D, E and F).

Regulatory authorities approached the regulation of medical products during the COVID-19 pandemic in four different ways. In general, the scope of emergency use authorization for most respondents was medicines, including vaccines and other biologics. The following respondents also included medical devices/in vitro diagnostics (IVDs) within their medicines/vaccines pathway: China, Germany, Japan, and the World Health Organization (WHO). Canada had a separate *Interim order respecting the importation and sale of medical devices for use in relation to COVID-19*. Several other countries (Colombia, Germany, Japan, Singapore, Switzerland and UK) also introduced or had specific legal provisions for authorisation during the pandemic.

Due to the lack of information provided by most respondents with respect to medical devices/IVDs, the following analysis focuses only on the names and types of authorizations with validity conditions for medicines, including vaccines and biologics.

Using existing legislation for approving medicines, including vaccines and biologics:

- European Union, Conditional marketing authorisation, Article 14a of Regulation (EC) No 726/2004 and Regulation (EC) No 507/2006 (with specific provisions for public health emergencies)

- Republic of Korea, Regulation on approval and review of biological products, MFDS Notification No.2021-29, Article 41 (Fast Track review, etc.)
- Saudi Arabia, conditional approval, created a new regulatory guideline to register COVID-19 vaccines

Using existing legislation in place to allow for emergency use without a marketing authorisation:

- European Union, Emergency use Art 5.2 of Directive 2001/83/EC, and Compassionate Use Article 83 of Regulation (EC) No 726/2004—at the Member State level
- Japan, Article 14-3 of the Pharmaceuticals and Medical Devices (PMD) Act
- United Kingdom, Temporary authorisation, Article 174 Human Medicines Regulations 2012
- United States, Section 564 of the FD&C Act (21 U.S.C. 360bbb-3)

Amending existing legislation to accommodate emergency use:

- China, “Administrative Measures for Drug Registration" (No. 46 of 2020)
- Singapore, Pandemic Special Access Route (PSAR), “emergency therapeutic product” through an interim authorisation under regulations 60A(4) and (5)(b) of the Health Product (Therapeutic Products) Regulations, and “emergency medical devices” through an interim authorisation under regulations 13C(4) and (5)(b) of the Health Product (Medical Devices) Regulations
- Switzerland, Temporary authorisation to use medicinal products in accordance with Article 9b para as a part of revision of the Therapeutic Products Act
- United Kingdom, Article 174A Human Medicines (Coronavirus and Influenza) (Amendment) Regulations 2020 (SI 2020/1125)

Introducing new legal rules to address the emergency use:

- Canada, Interim Order Respecting the Importation, Sale and Advertising of Drugs for Use in Relation to COVID-19 and then transition to amended *Food and Drug Regulations*
- Colombia, Decree 1787 of 2020
- Germany, Ordinance assuring the supply of products for medical needs for the population in the context of the epidemic caused by the coronavirus SARS-CoV-2 (MedBVSV)).

Similarities/Common approaches

Most jurisdictions have legal provisions for specific, time-limited authorisation approaches applicable to COVID-19 pandemic. Naming most commonly refers to either the temporary or conditional nature or the emergency context of the authorisation and in some instances may refer to allowing importation and/or use of unauthorised product. Provisions are usually applicable to medicinal products (including also biological products and vaccines) for prevention or treatment of COVID-19, but in some regions (Canada, China, Japan, Singapore) may also include medical devices and in vitro diagnostics.

Duration of authorisation typically is either:

- a fixed duration (most commonly 1 year), linked with duration of the emergency situation and the public health needs for the product concerned, affected by changes in the benefit/risk balance of the product concerned, and/or
- linked with the generation of sufficient data for granting of a 'regular' marketing authorisation.

Termination of the authorisation is either though adoption of an administrative act on its revocation, or though expiry.

Switzerland revised its *Therapeutic Products Act* to allow for a temporary authorisation that is valid for a maximum period of two years. All documentation on the fulfilment of conditions must be submitted to Swissmedic for review within two years of the official approval decision for the temporary authorisation, together with an application for the granting of ordinary authorisation.

Canada and Colombia introduced new legal rules to address the emergency use. Canada's interim order temporary authorization is valid for only one year until the IO expires. The *Food and Drug Regulations* were amended to provide that an ISAD IO authorization will be revoked unless a submission is filed within:

- 90 days following the coming into force of the amendments, if the drug was authorized under the ISAD IO before the amendments came into force or
- 90 days following the issuance of an authorization under the ISAD IO, if the drug was authorized after the amendments came into force.

In Colombia, an ASUE granted by INVIMA is valid for one (1) year, counted from the date of the execution of the administrative act. It may be renewed only once for the same term, with the presentation of the respective application, in the terms and conditions indicated in the Decree 1787 of 2020, and in accordance with the schedule presented by the applicant, and approved by INVIMA, who will monitor it.

Similar to the one-year temporary authorisation offered by some NRAs, the WHO offers an Emergency Use Listing (EUL) for access to vaccines, therapeutics and IVDs to low- and middle-income countries (LMIC). The EUL is valid for a period of one-year and can be extended, if necessary.

Singapore created a Pandemic Special Access Route (PSAR) with an interim authorisation, similar to Canada's approach. Companies are required to file an application to transition the product from the PSAR interim authorisation to a full registration, once sufficient data is available, while in Canada companies can file for a full notice of compliance under the amended *Food and Drug Regulations*.

The UK allows for an R174 temporary authorisation that is valid until it is either expressly withdrawn by the MHRA or the MHRA issues a full marketing authorisation (MA).

Unique features

Germany's approach was to issue an Ordinance granting exemption from certain provisions of the German Medicinal Products Act. No conditional/temporary/emergency use authorisation was granted. The applicability of the MedBVSV is limited in time. It ceases to be in effect when the German Bundestag declares the epidemic situation of national importance to be over. The temporary supply/placing on the market of medicinal products without market authorisation based on the MedBVSV is no longer possible as of the date the MedBVSV ceases to be effective.

In Japan, the validity of Special Approval for Emergency is until the time when the Minister for Health, Labour and Welfare withdraws the approval in a case when the conditions of the eligibility criteria no longer persists or withdrawal is necessary to prevent damage to the public health.

In China, the validity is case-by-case and depends on the duration required to complete the post approval commitments.

Implementation enablers

Both the EU and the Republic of Korea used existing regulatory mechanisms for a **conditional market authorisation**. Both allow for fast-track review and approval with the provision of some data after product approval. In the EU the framework has specific provision for public health emergencies, allowing also the non-clinical and pharmaceutical (quality) data to be less comprehensive than usual, subject to fulfillment of defined criteria for authorisation. In the EU, this type of authorisation is valid for one year and is renewable, while in the Republic of Korea, it is valid for five years.

Saudi Arabia used a conditional market authorisation approach with the creation of a new regulatory guideline to register COVID-19 vaccines which allows the company to submit portions of the regulatory application to the SFDA as they are completed.

The United States has the ability to issue an emergency use authorization pursuant to Section 564 of the FD&C Act (21 U.S.C. 360bbb-3). The policy for the EUA for Vaccines to Prevent COVID-19 is in effect for the duration of the pandemic. Note: Issuance of an EUA for a COVID-19 vaccine is not based on the public health emergency (PHE) declaration and may remain in effect beyond the duration of the PHE declaration if all other statutory conditions are met.

Implementation limitations

Japan's Priority Review was also available with validity the same as a general approval. The implementation limitation for priority review is that there is no rolling review, and the safety, efficacy and quality requirements are the same as for a regular review.

The implementation limitations for Canada's ISAD IO were that it expires within one year and the *Food and Drug Regulations* needed to be amended swiftly to continue access to the vaccines and treatments approved under the ISAD IO.

While the duration of the authorisation is often limited by a fixed time period and can be revoked in case of a change to the benefit-risk balance of the product. In some jurisdictions, the validity of the authorisation is not necessarily linked with changes in the environment, such as improvement in the pandemic situation or the availability of potentially better candidates. This could increase hesitancy to grant these authorisations, if there are doubts about ability to act swiftly when circumstances change regarding the urgent public health need.

Overall observations (key take home messages)

Additional emergency measures taken by countries to provide an authorization for COVID-19 medicines and vaccines in the context of a pandemic were based on the regulatory environment of the country when the pandemic hit. For some, existing regulatory frameworks could be used, while others needed to develop interim measures quickly. Having a regulatory framework that is poised to address future pandemics would address some limitations encountered with respect to validity and transitioning. Each NRA will have lessons learned to further improve their response during a future pandemic.

Additional comments

"WHO's Emergency Use Listing (EUL) is a prerequisite for COVAX Facility vaccine supply. It also allows countries to expedite their own regulatory approval to import and administer COVID-19 vaccines."[53]

Eligibility criteria and submission, evaluation and authorization requirements

Description

This is the overall analysis of eligibility criteria and submission, evaluation and authorization requirements based on data from Part A Facts (columns H, I, J, K, L, M, N).

Eligibility Criteria

Similarities/Common approaches

The similarities/common approaches were divided fairly evenly amongst the regulators who responded. There was no one approach that was the most common.

When regulators have existing emergency use regulatory provisions, these are capable of being used in a public health emergency, including a pandemic, to approve a health product if the general criteria is met for the unmet medical need, public health emergency or pandemic. The European Union—at

Member State level, Republic of Korea, United Kingdom (R174) and the United States all had existing legislation that could be used during the COVID-19 pandemic.

Some regulators amended their existing legislation to accommodate emergency use by describing an urgent public health need, by designating health products required during a pandemic or by providing specific criteria the medicinal product must meet. These types of amendments were undertaken by China, Singapore, Switzerland and the United Kingdom (R174A).

For NRAs that chose to introduce new legal rules to regulate the emergency use of COVID-19 medicines, including vaccines and other biologics, the use of the term COVID-19 or SARS-CoV-2 was used when defining the scope and eligibility criteria. These regulatory efforts were undertaken by Canada, Colombia and Germany.

Unique features

Implementation enablers

The European Union, at the regional level, can enable access to a medicine during an emergency through a (1) conditional marketing authorisation, while at the Member State level, access can also occur through (2) emergency use, and (3) compassionate use. The emergency use article is further defined at the national level and can be tailored for the emergency situation.

Japan has unique eligibility criteria where an unapproved medical product can be used after being given Special approval for emergency if the following criteria are met:

1. Emergency situation requires an unapproved medical product to be used to prevent damage to the public health caused by the spread of diseases,

2. Emergency situation cannot be managed appropriately by any means other than the use of the unapproved product, and

3. Product is legally available in a country with a regulatory system for medical products that is equivalent to Japan.

Implementation limitations

The nations who introduced legal rules specific to COVID-19 medicines, including vaccines and other biologics are limited in applying those rules to only those medical products. Any new pandemic would necessitate a need to revisit regulatory requirements and determine the best course forward for approving medicines, including vaccines and other biologics for an urgent public health need.

Differences in technical requirements and procedures from usual (full) MA pathway

Similarities/Common approaches

All of the regulatory authorities who responded based the decision for the emergency authorization on minimum safety, quality and efficacy data to conclude a positive benefit/risk assessment. Guidance on safety, efficacy and quality requirements for COVID-19 vaccines were published by Health Canada, the EMA, Japan, Singapore, Switzerland, and the USA.

It is recognized by regulatory authorities and the WHO, that clinical studies are on-going and that the applicant will provide comprehensive S/E/Q data in the future.

Unique features

China took a comprehensive approach to develop a guiding principle to encourage clinical value-oriented drug innovation and to accelerate the marketing of clinically urgently needed drugs with outstanding clinical value, in accordance with the "Drug Administration Law of the People's Republic of China," "The Vaccine Management Law of the People's Republic of China," and "The Traditional Chinese Medicine Law of the People's Republic of China." The "Administrative Measures for Drug Registration" draws on international experience and combines the practice of drug review in China to formulate the guiding principle "Technical Guidelines for Conditional Approval and Marketing of Drugs" released by the Center for Drug Evaluation of the State Drug Administration.

Implementation enablers

The work by the International Coalition of Medicines Regulatory Authorities (ICMRA) through SARS-CoV-2 workshops to discuss safety, efficacy and quality requirements was a significant contributor to accelerating the development of minimum S/E/Q data requirements by NRAs. For regulatory authorities who have a conditional approach in their regulatory framework to progress to a full MA, the provision of complete S/E/Q data in the future is facilitated.

Implementation limitations

The interim order approach with a one-year expiry date by Canada is a temporary emergency authorization. Although data can be provided while the interim order is in force, it cannot be provided once the authorization expires with the expiry of the IO, unless the manufacturer has made a new drug submission through the transition measures introduced in the amended *Food and Drug Regulations*. The submission under the FDR enables the manufacturer to provide S/E/Q data as defined by regulatory requirements and to complete the data according to terms and conditions as described in a plan. The process of making a submission to transition from the interim order to the *Food and Drug Regulations* is limited to a 90-day period.

Provision for rolling/progressive review

Similarities/Common approaches

Most of the respondents implemented a rolling/progressive review for COVID-19 drugs when an application was made during the pandemic under a specific regulatory pathway that enabled a rolling review.

Yes: Canada, China, Colombia, EU (Conditional MA), Kingdom of Saudi Arabia, Republic of Korea, Singapore, UK, US

No: Germany, Switzerland, Japan

Note: Japan has no legislation for a rolling review, but a substantial rolling review is conducted through prior scientific advice.

Implementation enablers

Regulators introduced varying implementation enablers for the rolling/progressive review:

- Required manufacturers to provide an application plan describing the studies to be completed and the timing of the planned submission, with data for Modules 3-5 submitted as it becomes available.
- Requirement for Modules 1 and 2 of the CTD at filing.
- The EU applied the rolling review in the public health emergency context, under the Conditional marketing authorisation pathway, as there is no explicit provision in legislation.

Implementation limitations

The EU's Emergency use (Art 5.2 of Directive 2001/83/EC) has not been used for a rolling review at the EU level, although it may exist at the national level. The rolling review route may be available based on limited data under emergency use, however, stepwise assessment may be less important.

The EU's Compassionate use programme does not use a stepwise (rolling review) approach.

Enhanced discussions with sponsors

Similarities/Common approaches

Most NRAs encouraged enhanced discussion with sponsors.

Yes: Canada, China, Colombia, EU (Conditional MA), Germany, Japan, Kingdom of Saudi Arabia, Singapore, Switzerland, USA

Unknown: Republic of Korea

Unique features

The enhanced discussions with sponsors can vary between jurisdictions.

In addition to strongly encouraging early and ongoing discussions with sponsors to ensure that regulatory requirements are met, Health Canada also encourages sponsors to contact Health Canada for discussion and meetings specifically related to the topic of labelling.

In addition to advising that applicants should communicate with the Drug Evaluation Center regarding the clinical trial design and clinical trial results that support conditional approval, China's NMPA encourages applicants to communicate before carrying out clinical trials and before applying for conditional approval for marketing.

In addition to advising sponsors to contact the US-FDA as soon as possible to discuss expectations and considerations for the sponsor's particular vaccine, the FDA also recommends early communication on facility issues.

Implementation enablers

In the EU, enhanced dialogue with sponsors occurs from a very early stage through to assessment and post-approval during the public health emergency (no explicit provision in the legislation).

Plans for the use of medicinal products would normally be discussed at the national level, if approval was sought through the EU's Emergency use or Compassionate use programme. For COVID-19 products, the EMA is open to engage with all developers irrespective of the regulatory route intended.

Enhanced transparency measures

Similarities/Common approaches

For the NRAs that did apply enhanced transparency measures, their websites provide an unprecedented level of detail with respect to COVID-19 and actions taken to mitigate it. This included committing to a transparent authorization process.

Yes: Canada, EU, at a national level in the EU as well for emergency use and compassionate use, Japan, Kingdom of Saudi Arabia, Singapore, Switzerland, UK, US

No: Germany

Unknown: China, Colombia, Republic of Korea

Unique features

The EU provided exceptional transparency measures for COVID-19 medicines by publishing information it does not normally publish for other medicines, including:

- List of medicines that have received scientific advice or guidance from COVID-ETF published
- Full body of the RMP (plus Annex 4)
- News announcement of application for extension of indication
- Monthly safety updates for approved COVID-19 vaccines and ad-hoc as needed[54]

The US FDA committed to a transparent authorization process:

- Briefing documents to be posted on the web
- Public advisory committee meetings being livestreamed
- EUA review memo posted on the web
- FDA will brief interested parties and answer questions

Implementation enablers

Government support and direction for enhanced transparency measures, as these require a high level of resources to implement daily.

Implementation limitations

Enhanced transparency measures take a great deal of effort and human resources well beyond normal transparency measures. Enhanced transparency measures can provide essential information in a timely manner. For example, expedited publication of rationale for decision, information related to safety issues and publication of clinical data. Adequate human resources are necessary to sustain this level of transparency.

Overall observations (key take home messages)

The pandemic could be a catalyst for some countries to enhance both transparency measures and engagement with industry beyond the pandemic. This would be in line with the WHO's recently released guidelines on principles of Good regulatory practices (GRP) and Good Reliance Practices (GRelP). See Annex 10 and Annex 11 of the WHO's Fifty-fifth report on WHO Expert Committee on Specifications for Pharmaceutical Preparations.

Other

Similarities/Common approaches

Unique features

For the EMA's Conditional Market Authorisation: Normally only the clinical data can be less comprehensive than normally required, but in case of a public health emergency also the non-clinical and/or quality (pharmaceutical) data may be less comprehensive.

Implementation enablers

The evaluation the German NRA is obliged to perform according to the MedBVSV has to be a full evaluation of all available data. Assessment reports, certificates etc. from other NRAs can be used as supporting documentation.

Requirements for authorisation

Similarities/Common approaches

Benefits are greater than the risks/positive benefit-risk balance/positive benefit-risk ratio (Canada, China, Colombia, EU, Germany, Japan, Singapore, USA, and WHO).

Unique features

Standard used for EUA: product "may be effective" and its "known and potential benefits outweigh the known and potential risks." EUA may be appropriate once studies have demonstrated the safety and effectiveness of the vaccine but before manufacturer has submitted and/or FDA has completed its formal review of the biologics license application. EUA application evaluation includes public advisory committee.

Implementation enablers

In the case of an emergency use authorisation, nations have put enabling measures in place to mitigate risk so that a vaccine can be approved in a timely manner to meet the current UPHN (urgent public health need):

- all additional information and material must be submitted (Canada)/it is likely that the applicant will be able to provide comprehensive data post-authorisation (EMA)
- applicant has committed to additional measures needed to mitigate risks and address information gaps taking into consideration the uncertainties related to the drug in the context of an UPHN related to COVID-19 (Canada)/ The MAH must carry out new or ongoing clinical trials in accordance with the specific conditions attached to the drug registration certificate. (China)/ compliance with conditions set by INVIMA including completion of ongoing studies, RMP and PV strategies (Colombia)/ (c) the medicine fulfils an unmet medical need; (d) the benefit of the medicine's immediate availability to patients is greater than the risk inherent in the fact that

additional data are still required. (EMA)/ ability of sponsor to provide results of ongoing and additional clinical trials post-authorisation (Japan).

Implementation limitations

The EU's Emergency use (Art 5.2 of Directive 2001/83/EC): Criteria is set at national level and a case-by-case approach may be applied depending on the particular circumstances of the public health emergency.

The EU's Compassionate use: All available evidence to be reviewed that can support use in-patient without available treatment alternatives and not included in clinical trials, on a compassionate basis. For efficacy may rely on promising early data observed in exploratory trials.

Post authorization commitments/requirements

Description

This section provides an analysis of post-authorization commitments and requirements based on data from Part A Facts (columns O, P, Q, R, S).

Post-authorization regulatory obligations are a well-established element of a life-cycle approach that provides for a reassessment of a product's benefit-risk based on the accumulation of safety and effectiveness information in real world conditions. Within the context of accelerated COVID-19 product development and authorization, the continued accumulation of safety and efficacy data from ongoing or planned clinical trials is essential to filling knowledge gaps and confirming that expected benefits outweigh known and potential risks. Furthermore, there is a need to ensure the quality and consistency of manufacturing, further validate approved shelf-life and storage conditions from longer-term stability studies and support post-approval changes.

Similarities/Common approaches

Post-authorization obligations are established on a case-by-case basis as part of the emergency use or conditional marketing authorization, but at a minimum generally include the following:

- The completion of ongoing and planned studies to confirm the benefit-risk profile leading to a full marketing authorization (and prequalification in the case of WHO). This includes collecting data from ongoing placebo-controlled trials for as long as feasible.
- Post-authorization safety activities as defined in the risk management plan (RMP) which may include enhanced surveillance and post-authorization safety studies in addition to passive surveillance and risk minimization measures.
- The submission of results from ongoing CMC studies, such as stability data.

- Independent batch release by the NRA for vaccines and other biologicals. A number of respondents indicated that this would include testing on all batches.

Most respondents confirmed that post-authorization obligations were legally binding. Non-compliance with conditions could result in revoking the authorization and, where provided, other regulatory actions (such as levying fines in the case of EC/EMA).

Most authorities have also established timelines for the reporting of post-authorization information, with the requirement to report on progress towards meeting targets.

Unique features

Some of the NRAs required or mentioned further data/commitments such as:

- The filing of monthly safety reports for COVID-19 vaccines in addition to the 6-month PSURs.
- Implementation of traceability measures (for all biologicals, including vaccines).
- Monitoring the impact of new mutations in viral genome on performance of COVID-19 tests.

Additional exceptions noted include:

- EU: EUA at national level cannot be converted into a 'regular' or conditional marketing authorisation.
- Germany: As no issue of a conditional/temporary/emergency use authorization is granted, the Ordinance (MedBVSV) does not contain provisions for post-approval commitments / requirements. However, for the medicinal products without a marketing authorization that are distributed/placed on the market based on the MedBVSV, all pharmacovigilance provisions of the German Medicinal Products Act apply without exception.
- Canada:
    - Given the choice of regulatory instruments (time-limited Interim Order), completing full studies under the ISAD IO does not result in a full MA. A new drug submission still needs to be made under the *Food and Drug Regulations* within specified timelines, and studies would need to be completed as per terms and conditions issued under the FDR.
    - Health Canada's lot release program categorizes lots of COVID-19 vaccine as Group 3 with different requirements depending on the product. Based on the outcomes of the review some sponsors are required to notify Health Canada of the lots to be distributed to Canada, supply a COA (Certificate of Analysis) and the number of doses. Other sponsors require a lot release letter following protocol review prior to distribution.

Implementation enablers

- Regulatory provisions (legally binding post-authorisation obligations)
- Adequate capacity and competent staff to carry out post authorization oversight (laboratory capacity, review of safety data, review of ongoing clinical trial data)
- Regulatory networks and collaborative arrangements
- Transparency in establishing post-authorization obligations
- Manufacturer's consent, confidentiality agreements and secure information-sharing platform and mechanisms (WHO)

Implementation limitations

- Lack of enablers cited above
- Time pressures and ability of manufacturers to respond to different regulatory requirements
- Feasibility of conducting placebo-controlled trials in the face of increased vaccine rollout in countries
- Approved/authorized product based on full recognition or import permit without access to primary information or lack of agreements between NRAs and consent of MA holders.

Overall observations (key take home messages)

- The ability and authority to set and enforce post-authorization obligations are essential to early authorization and availability of COVID-19 products while also ensuring appropriate confirmatory studies and ongoing monitoring to address knowledge gaps.
- Post-authorization obligations are set on a case-by-case basis, however generally include the commitment to complete ongoing and planned studies to confirm the benefit-risk profile, safety activities defined in risk management plans, and batch release/testing for vaccines and other biologicals.
- While most authorities expect sponsors to apply for a full MA when supported by data the process for doing so differs between countries, reflecting the uniqueness of regulatory environments.
- Transparency of post-authorization obligations and the sharing of information related to ongoing studies are important in promoting greater convergence and more-informed, risk-based regulatory measures. This is particularly prevalent when regulators rely (in part or full) on other regulatory authorities or WHO.

Additional comments

While not a focus of the deep dive, a common working definition of post marketing requirements (e.g., required under regulations) and post marketing commitments (e.g., studies a sponsor has agreed to conduct, but that are not required by a statute or regulation) may be useful.

Product status/impact on ongoing placebo controlled clinical trials

Similarities/Common approaches

This is the overall analysis of product status on ongoing placebo-controlled trials based on data from the Deep Dive questionnaire.

Although the legal frameworks for emergency use differ in each country and region, initiating a Phase 3 trial is essential. The regulatory decision is based on the results of interim analysis considering the emergency situation.

At present, placebo-controlled trials (PCT), used as conventional clinical trials, have been required because there is no guidance for alternatives to PCT in Phase 3 trials at the timing of this survey.

Unique features

For the clinical evaluation of current COVID-19 vaccines, while the information required for emergency use differs in each country and region, the data set and their quality for the first or the second approvals seem to affect following approvals in other countries.

There are cases where the vaccines developed in some countries do not proceed to review in other countries. It will be important to conduct a factor analysis of these cases toward future development of vaccines for emergency use with respect to scientific evidence and requirements.

Implementation enablers

When applicants seek to conduct clinical trials, it is significant for the applicants to consult with regulatory authorities at an earlier stage.

Implementation limitations

Presently, applicants need to collect necessary data by consulting with regulatory authorities. Placebo-controlled trials in Phase 3, which are standard trials, are becoming unfeasible. Alternative methods to placebo-controlled trials need to proceed under the context of a common global understanding.

Overall observations (key take home messages)

- There is a need to make a global common request for necessary information on efficacy and safety, while the legislation for emergency use differs in each country/region.
- Placebo-controlled trials are becoming unfeasible. Global regulators should discuss/evaluate alternative methods from placebo-controlled trials and harmonize them internationally.

Deep dive report on the review of provisions and procedures for emergency authorization of medical products for COVID-19 among ICMRA members - July 2021

Reliance provisions and approaches

Description

This section provides an analysis of reliance provisions and approaches based on data from Part A Facts (column T).

In conducting an analysis of responses, it is important to have a common understanding of the term reliance. For the purpose of this review, the WHO definition of reliance has been applied: 'The act whereby the regulatory authority in one jurisdiction takes into account and gives significant weight to assessments performed by another regulatory authority or trusted institution, or to any other authoritative information, in reaching its own decision...' (WHO guideline on *Good reliance practices in the regulation of medical products: high level principles and considerations*, Annex 10, Technical Report Series 1033).

According to the above definition, regulatory authorities may be grouped across three categories based on responses concerning the ability to rely on foreign regulatory authorization for certain elements of review of COVID-19 products, as presented below. However, the situation is both mixed and nuanced, even for a given respondent. A fuller appreciation of the extent to which reliance and collaboration were factored into regulatory response planning and played a role in the pandemic requires further discussion and information. Furthermore, information and reports from other regulatory bodies may be used as supportive of reviews even if not used to reduce the extent of review, as noted in the case of Germany.

While not explicitly captured in responses to the EUA deep dive questionnaire, information-sharing and collaboration among regulatory agencies and international organizations has also been an important feature of the response to the pandemic, as further described below. Existing agreements and procedures, such as those related to GMP certifications and joint inspections, would also continue to be important in facilitating emergency authorizations during the pandemic.

Jurisdictions and organizations with an ability to rely on foreign regulatory authorization for certain elements of the review of COVID-19 products:

Canada	The *Interim Order Respecting the Importation, Sale and Advertising of Drugs for Use in Relation to COVID-19*: Section 4 provides for authorizing a drug based on certain elements being authorized by a foreign regulatory authority. Drugs must be included on the List of Foreign Drugs and authorized for sale in a foreign jurisdiction.
Colombia	Sanitary Authorization for Emergency Use (through Decree 1787 of 2020) provides for reliance on listed recognized authorities from 'High Health Surveillance OECD member countries' and WHO.

Singapore	The evaluation process under PSAR may take into consideration any prior authorisation issued by HSA's reference agencies.
Switzerland	Reduced assessment under application of Article 13 Medicinal products and procedures authorised in foreign countries, TPA is possible for an application for temporary authorization for regulators on list of countries with comparable human medicinal product control MHV4.
UK	• In relation to ACCESS countries. • Unique to EU/UK: European Commission (EC) Decision Reliance Route
WHO	Provisions for Abridged Procedures described in *Emergency Use Listing Procedure* (Version 13 December 2020). Global assessment model to facilitate in-country authorizations based on EUL described in product evaluation roadmaps for COVID-19 vaccines.

Jurisdictions that do not have the ability to rely on foreign regulatory authorization for certain elements of the review of COVID-19 products:

- China
- Germany
- Kingdom of Saudi Arabia
- Republic of Korea
- USA

Jurisdictions with a mixed scenario:

- EU:
  - Not provided for at the Community level (i.e., centralised procedure)
  - Reliance not explicitly foreseen but not excluded at national level through Emergency use (Art 5.2 of Directive 2001/83/EC) and Compassionate Use (Article 83 of Regulation (EC) No 726/2004).
- Japan:
  - No provisions for reliance under Priority Review
  - Activation of Special Approval for Emergency requires the product to be legally available in a country with a regulatory system for medical products that is equivalent to Japan through designation by the Cabinet Order.
- UK:

- There is a European Commission (EC) Decision Reliance Procedure in effect, where "for a period of two years when determining an application for a Great Britain Marketing Authorisations (MA), the MHRA may rely on a decision taken by the European Commission (EC) on the approval of a new MA in the centralised procedure."[55]

Similarities/Common approaches

Of those authorities and organizations that have an ability to rely on other authorities for the review (or eligibility for emergency authorization) of COVID-19 products, most stipulated the requirement that the reference agency have a 'comparable/equivalent regulatory system' or 'level of control' or be a 'high health surveillance' country. (Note: while there was some overlap in the list of reference countries/regions cited, there was also significant diversity.)

Unique features

Japan: Product availability in a country with an equivalent regulatory system set as a condition for triggering the SAE pathway.

WHO: The Prequalification program relies whenever possible on the safety, efficacy and quality evaluations of other internationally recognized regulatory authorities and agencies ('WHO Listed Authorities'), focusing its efforts on programmatic considerations aimed at ensuring the suitability of products, packaging, labelling and—for medicines and vaccines—pharmacovigilance plans and risk minimization measures in low- and middle-income countries (LMICs). This practice has also been prominent in the emergency use listing of a number of COVID-19 vaccines.

In order to accelerate vaccine authorizations at country level through reliance on the EUL, regulatory roadmaps were developed that included agreements with the NRAs of record responsible for the emergency use authorization of the vaccine to discuss information and the sharing of reports; the involvement of subject matter experts from NRAs in different regions in the global assessment process; the sharing of product dossiers and WHO EUL reports with NRAs via a secure WHO electronic site with the consent of manufacturers and signed confidentiality agreements; and engagement with NRAs to promote use of the WHO EUL, discuss critical aspects of the review, and address any bottlenecks. This global regulatory innovation also obviated the need to file applications in many LMICs and has resulted in regulatory authorizations in over 100 LMICs, many within 15 days of issuing an EUL.

WHO/PAHO: As noted by Colombia in relation to special import provisions, PAHO has established a framework and mechanism for accelerating in-country approvals and ensuring the quality of products purchased under the PAHO Revolving Fund, including COVID-19 vaccines. Prequalification or Emergency Use Listing by WHO is a condition of purchase and supply.

Colombia: In addition to special import authorization through PAHO, provisions for full (in addition to partial) reliance on reference authorities or WHO for issuance of emergency use authorization.

Under the broader umbrella of regulatory collaboration:

Collaborative review:

Access Consortium (Australia – Canada – Singapore – Switzerland – UK): It is also possible for a manufacturer to ask for an authorisation application to be reviewed within the framework of the work-sharing initiative of the Access Consortium. The participating authorities coordinate the review of the corresponding applications, which must be submitted in at least two of the five possible countries.

Canada: Collaborative review with international regulatory partners is possible in cases where manufacturers file a rolling submission simultaneously with Health Canada and another jurisdiction with which there is a collaborative agreement.

EMA's OPEN (Opening our Procedures at EMA to Non-EU authorities) pilot: Pilot in December 2020 to increase international collaboration on the evaluation of COVID-19 vaccines and therapeutics. Objective: to allow active international participation in the scientific evaluation of COVID-19 products where confidentiality arrangements are in place with non-EU regulatory authorities and selected international organizations (including WHO)—in line with the principle of reliance and global good regulatory practices. Goal: accelerate development and assessment of COVID-19 products and bring in additional expertise and resources where needs and products are the same. Health Canada, WHO participating (through which NRAs from LMICs are also involved).

Implementation enablers

- Regulatory provisions for reliance
- Similar technical requirements
- Same product
- Transparency—a practice essential for building public trust and enabling international cooperation and reliance through better knowledge of the regulatory system.
  Examples of enhanced measures implemented in the context of COVID-19 include:
    - Dedicated website/pages
    - Publicly available information on the review process and requirements, review status, advisory committee briefing materials, decisions (including negative) and the basis for decisions
    - Full RMPs (posted or available on request)
    - Public advisory committee meetings
    - Briefing of other regulatory authorities

    - In addition to routine measures, such as public assessment reports, Freedom of Information requests, etc.
- Work-sharing arrangements
- Ability to share non-public regulatory information subject to confidentiality agreements and consent of manufacturers
- Secure electronic platforms.

Implementation limitations

- Lack of enablers cited above
- Time pressures (both a possible limitation and an enabler, for example, for many LMICs).

Other limitations, including for countries with the ability to rely on foreign review reports, would require a retrospective assessment from regulators. For example, Canada in not carrying provisions forward from the Interim Order to the *Food and Drug Regulations*.

Overall observations (key take home messages)

- While the extent to which reliance on the authorization decisions and supporting information of other regulatory organizations played a role in the pandemic response is unknown (with the exception of WHO), having regulatory provisions enabling reliance, or at least not prohibiting reliance, provides additional tools in addressing the challenges posed by the pandemic. Further retrospective analysis would be needed to determine how provisions and practices could be improved.
- Near real-time information sharing and joint collaboration among regulatory authorities and WHO has been valuable in informing respective regulatory decisions, requirements, communications and plans related to COVID-19 products, notably through ICMRA policy and working groups.
- The EMA's OPEN pilot provided a valuable opportunity to collaborate and contribute to the broader assessment and authorization of COVID-19 products.
- Enhanced transparency measures introduced by a number of regulators to build public confidence in the safety, efficacy and quality of COVID-19 products also serve to promote reliance in the regulatory community.
- The WHO model for global assessment and facilitated in-country authorization has proven successful in accelerating access to quality-assured COVID-19 vaccines, particularly in LMICs.

Additional comments

Most respondents were not in a position to confirm the number of authorities that rely on them.

Deep dive report on the review of provisions and procedures for emergency authorization of medical products for COVID-19 among ICMRA members - July 2021

Acronyms and Initialisms

AMC	advance market commitment
CTD	common technical document
CRO	contract research organization
CRP	Collaborative Registration Procedure
EUL	emergency use listing
GMP	Good Manufacturing Practices
IVD	in-vitro diagnostic
LMIC	low- and middle-income countries
MAH	Market Authorisation Holder
NRA	National Regulatory Authority
QMS	Quality Management System
PAHO	Pan American Health Organization
PEG	product evaluation group
PHE	public health emergency
PHEIC	public health emergency of international concern
PIL	Patient Information Leaflet
PQ	pre-qualification
PSUR	Periodic Safety Update Report
RMP	risk management plan
SAE	Special Approval for Emergency
SPC	Summary of Product Characteristics
TAG	technical advisory group
TPP	Target Product Profiles
UN	United Nations
WHO	World Health Organization

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