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WHO-listed authority (WLA) framework

PERFORMANCE EVALUATION SUMMARY REPORT

**European Medicines
Regulatory Network (EMRN)
EUROPE**

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Note: For a full list of abbreviations used in the following report, please refer to the Operational guidance for evaluating and publicly designating regulatory authorities as WHO-listed authorities and the Manual for performance evaluation of regulatory authorities seeking designation as WHO-listed authorities.

1. OVERALL SUMMARY

On December 29th, 2022, the European Medicines Regulatory Network (EMRN), represented by the Heads of Medicines Agencies Management Group (HMA-MG) and the Benchmarking of the European Medicines Agencies Steering Group (BEMA SG), expressed interest in being designated by WHO as a WHO-Listed Authority (WLA) following the applicable WHO process and methodology, for both product streams -medicines [including multisource (generics) and new medicines (new chemical entities), biotherapeutics and similar biotherapeutic products] and vaccines- thus requesting the performance evaluation (PE) of all regulatory functions, for all regulatory authorities included in the network.

The European Medicines Regulatory Network (EMRN) is a regional regulatory system (RRS) composed of the European Commission, the European Medicines Agency and the medicines regulatory authorities from 30 European Economic Area (EAA) countries (27 EU Member States: Austria, Belgium, Bulgaria, Croatia, Cyprus, Czechia, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain and Sweden, and 3 EFTA Member States: Iceland, Liechtenstein and Norway).

Members of the network share a common regulatory framework, which is underpinned by a common legal framework, thus complying with the definition and criteria set out by WHO to be considered as a single entity (SE).

In addition, the EMRN is currently included in the list of transitional WLAs, being considered a Stringent Regulatory Authority (SRA) for medicines and a “highly performing Regulatory Authority” for vaccines.

Based on the above, the EMRN is considered eligible for the abridged evaluation pathway towards listing as WLA, and, being a single entity, all NCAs of the network can achieve listing through the same performance evaluation (PE) process.

A roadmap was drawn jointly by WHO and EMRN, which entailed the piloting of the WLA framework applied for the first time to a regional regulatory entity.

Following the abridged evaluation pathway, it was concluded that the EMRN successfully met all criteria established for WLAs and recommended for listing the European Commission, the EMA and all NCAs of the network in all functions, for the product stream of medicines [including multisource (generics) and new medicines (new chemical entities), biotherapeutics and similar biotherapeutic products], and vaccines.

2. INTRODUCTION AND CONTEXT

2.1. BACKGROUND

The EMRN is based on a closely coordinated regulatory network of national competent authorities in the Member States of the European Economic Area (EEA = 27 EU Member States + 3 EFTA Member States: Iceland, Lichtenstein and Norway), working together with the European Medicines Agency (EMA) and the European Commission (EC), and following the same pharmaceutical legislation.

Note: Kingdom of Liechestein is a EU Member State, but it is not one of the WHO Member States.

In this network, parties have different roles as briefly set out below:

- The **European Commission** grants EU-wide marketing authorizations (under the centralized procedure) following scientific assessment by the EMA. It also monitors and oversees the network's activities. In addition, it is responsible for ensuring that EU law is applied correctly.
- The **EMA** is responsible for the scientific evaluation, supervision, and safety monitoring of medicines in the EU. The EMA also coordinates scientific expertise, including inspections, from across the EU.
- The **national competent authorities** are responsible for granting national marketing authorisations (through the national procedures) and supervising medicines in the respective Member States. They also provide expertise to the network.

All network members work closely with the EMA and the EC and with all other stakeholders involved in developing, manufacturing, distributing and administering medicines. This collaboration aims to ensure that the objectives of the common legislation are achieved.

Here below a more descriptive overview of the structure and line of authority of the European medicines regulatory network components:

The European Commission (EC) plays a key role in the regulation of medicines in the European Economic Area (EEA), which includes the European Union (EU) member states as well as Iceland, Liechtenstein and Norway. The Commission's responsibilities include:

- Developing and proposing legislation (right of initiative): The Commission proposes new laws and regulations related to medicines regulation and works with other EU institutions to ensure that they are adopted. The Commission is also responsible to ensure that the EU legislation is adequately implemented (enforcement). Ultimately, the EU courts are responsible for judicial review.
- Ensuring the safety, quality and efficacy of medicines: The Commission works closely with the European Medicines Agency (EMA) and national regulatory authorities to ensure that medicines are safe, effective, and of high quality. This includes monitoring the safety of medicines once they are on the market and taking EU-wide action when a safety issue has been identified for an authorized product (irrespective of the authorization procedure that was used) and when harmonized regulatory measures in all MS are considered necessary.
- Authorizing medicines: Based on the scientific assessments carried out by experts nominated by EEA Member States to EMA, the Commission grants or

refuses, changes or suspends marketing authorizations for medicines that have been submitted, via the above-mentioned centralized procedure.

- Global outreach: The Commission, working closely with the EMA, ensures appropriate collaboration with relevant international partners and promotes the EU regulatory system globally.

The **European Medicines Agency (EMA)** is a decentralized agency of the European Union (EU), and is the main regulatory body responsible for the scientific evaluation, supervision, and safety monitoring of medicinal products in the European Union (EU) and European Economic Area (EEA). It works closely with national competent authorities (NCAs) from EU/EEA Member States, which have their own regulatory bodies responsible for the authorisation, supervision, and monitoring of medicines at a national level.

EMA was established in 1995 by EU Regulation 2309/93, where the goal of the EMA was to coordinate the evaluation of scientific data associated with the approval, manufacturing, and inspection of medicines in the EU (24). This EU Regulation is dated Jul. 22, 1993 and has been subsequently amended by the European Parliament and Council, and is published as Regulation (EC) No 726/2004. The Executive Director of the European Medicines Agency is appointed by the Agency's Management Board in accordance with Regulation (EC) No 726/2004. The Management Board is composed of representatives of the EU Member States, European Commission, European Parliament, healthcare professionals and patients.

EMA works with the other members of the network on the following key activities:

- addressing key strategic issues for the European medicines regulatory network, such as the exchange of information and sharing of best practice;
- collectively, being responsible for common areas of medicines regulation, including marketing authorization procedures, in addition to the centralized procedure, in which more than one member state is involved (i.e., mutual recognition and decentralised procedures);
- focusing on the development, coordination and consistency of the European medicines regulatory network;
- supporting the network by providing high-quality professional and scientific resources, as well developing specific trainings curriculums at central level (EU-NTC) matching the training needs identified by member state agencies.
- providing a focus for making the most effective use of scarce resources across the network, such as developing and overseeing arrangements for work-sharing.

Within the EMA, several committees and working groups, composed of representatives appointed by individual member states, are responsible for different aspects of medicines regulation. For example, the Committee for Medicinal Products for Human Use (CHMP) is responsible for the scientific evaluation of medicines for human use; the Pharmacovigilance Risk Assessment Committee (PRAC) is responsible for the safety monitoring of medicines (regardless of their initial approval pathway, centralised or national); the Committee for Orphan Medicinal Products (COMP) is responsible for the evaluation of medicines for rare diseases; the Paediatric Committee (PDCO) is responsible for activities on medicines for children and to support the development of such medicines in the European Union; the Committee for Advanced Therapies (CAT) is

responsible for assessing the quality, safety and efficacy of advanced therapy medicinal products (ATMPs) and following scientific developments in the field.

In addition,

- the **Heads of Medicines Agencies (HMA)** is a network of the heads of the 'national competent authorities' (NCAs), the agencies responsible for regulatory oversight of human and veterinary medicines in the individual countries of the EU/European Economic Area (EEA). Heads and staff of national agencies are appointed according to national government civil service procedures.

The HMA provides a forum for the exchange of information and the development of regulatory policy, and it supports the implementation of EU medicines legislation at a national level. The HMA works to foster an effective and efficient European medicines regulatory system. It is supported by working groups covering specific areas of responsibility and by the Heads of Medicines Agencies Management Group and Permanent Secretariat. The European Medicines Agency is a member of the HMA.

- The **European Directorate for the Quality of Medicines and Healthcare (EDQM)** is a major administrative entity of the Council of Europe. The EDQM is a leading organisation that protects public health by enabling the development, supporting the implementation and monitoring the application of quality standards for safe medicines and their safe use which are recognised as a scientific benchmark and applied worldwide. The guidance and standards developed by the EDQM in the areas of blood transfusion, organ, cell and tissue transplantation and consumer health topics have a positive impact on public health in Europe and beyond.

All EU/EEA Member States are members of the Council of Europe and the European Pharmacopoeia Convention, which is a binding treaty, forming the legal basis of the work of the EDQM.

The official standards published within the EU Pharmacopoeia provide a legal and scientific basis for quality control throughout the lifecycle of a medicine, from development, through production and marketing.

The EDQM coordinates the General European Official Medicines Control Laboratories Network (GEON), which consists of full members (parties to the European Pharmacopoeia Convention) and associated members (observers to the European Pharmacopoeia Commission). The EU/EEA Network of Official Medicines Control Laboratories is a specific network of the GEON restricted to EU/EEA members, which performs market surveillance testing activities of medicines having undergone marketing authorisation via the centralised, mutual recognition or decentralised procedure. Furthermore, the Official Control Authority Batch Release (OCABR) Network, composed of EU/EEA members and states having signed a formal agreement which includes recognition of OCABR with the EU, performs Official Control Authority Batch Release of human biological medicinal products (blood and plasma-derived medicinal products and human vaccines) on behalf of the National Competent Authorities (NCAs).

The EDQM also coordinates the procedure for the certification of suitability to the monographs of the European Pharmacopoeia. The mission is to:

- assess and conclude suitability of monographs to control the chemical purity, microbiological quality and TSE risk (if relevant) for any substance covered by a European Pharmacopoeia monograph;
- check compliance at the manufacturing and/or distribution site(s) covered by Certificates of Suitability to the monographs of the European Pharmacopoeia (CEPs) with both Good Manufacturing Practice (GMP) for medicinal products for human or veterinary use and with the CEP granted according to the information submitted in the application(s) for CEP(s).

The above-described complex structure of EU/EEA medicines authorities is designed to ensure that medicines are safe, effective, and of high quality across the network. By working together based on the common legislation, these authorities help to ensure that patients across the EU/EEA have access to the medicines they need while also ensuring that those medicines are safe and effective.

In terms of previous recognitions, the European Commission is a Founding Regulatory Member in ICH, being also the only ICH supranational Regulatory Member. Owing to the common regulatory framework on pharmaceuticals that is applicable in all Member States of the European Union (EU) and the European Economic Area (EEA) EFTA states, all NCAs of the EMRN are considered stringent regulatory authorities (SRAs) for medicines (WHO Technical Report Series 1003), and as such included in the list of transitional WLAs.

Similarly, being considered by WHO as “exhibiting a high level of performance of WHO’s six recommended regulatory functions and exercising full regulatory oversight of any given vaccine”, EMA has been also included in the list of “highly performing NRAs” for vaccines.

Based on the above, EMA and countries in the EMRN has so far benefited for the facilitated prequalification procedure (abridged procedure) of human medicines and vaccines.

In 2019, EMRN was listed in the time-limited “WHO Interim List of National Regulatory Authorities”, as part of the planned transformation from the term Stringent Regulatory Authorities (SRAs) to WHO-Listed Authorities (WLAs); in March 2022, following the formal launching of the WLA initiative and the publication of the *Interim Operational Guidance for evaluating and publicly designating Regulatory Authorities as WHO listed authorities*, it was placed on the list of transitional WLAs and considered eligible for the abridged evaluation pathway towards listing.

It is also observed that the European medicines regulatory network:

- a) Established a benchmarking programme among the human medicines agencies known as the Benchmarking of European Medicines Agencies (BEMA), based on assessment of the systems and processes in individual agencies against a set of indicators agreed among member states.
- b) Established an audit programme among the GMP inspectorates of all EEA GMP human medicines agencies known as the Joint Audit Programme (JAP). JAP is based on assessment of the systems and processes in individual agencies against a set of indicators, which is recognized by PIC/S.
- c) Established a Mutual Joint Audit (MJA) and Mutual Joint Visit (MJV) programme of OMCLs to assess the compliance of laboratories in the network with the quality

requirements laid down in ISO/IEC 17025, the Network’s Quality guidelines and the European Pharmacopoeia.

2.2. OBJECTIVES AND SCOPE

Considering the WLA scope applied for by the EMRN, the objectives of the Performance Evaluation were to:

- Evaluate the performance of the EMRN (EC, EMA and NCAs) for the purpose of WLA designation as WLA for medicines, including multisource (generics) and new medicines (new chemical entities), biotherapeutics and similar biotherapeutic products, in all regulatory functions
- Evaluate the performance of the EMRN (EC, EMA and NCAs) for the purpose of WLA designation for vaccines in all regulatory functions

2.3. METHODOLOGY

As laid down in the *Operational Guidance for evaluating and publicly designating Regulatory Authorities as WHO-listed authorities*, the abridged evaluation pathway foresees a self-assessment of all regulatory functions by the candidate WLA and subsequent WHO desktop review against a set of pre-selected GBT sub-indicators and Performance Evaluation indicators, included in a specifically designed “abridged tool” (see Annex 6 of the PE Manual); none of the PE tools is instead foreseen in the abridged pathway, as alternative evaluation mechanisms recognized by WHO already exist and provide sufficient evidence of the performance of candidate WLAs in all functions (e.g., WHO prequalified products, emergency use listing products, PIC/S membership, participation in OMCL’s network).

As agreed during the planning phase, the initial self-assessment was conducted at central level, and inputs related to common provisions processes, and outcomes were coordinated and provided by the BEMA steering group, while during the evaluation phase, a risk-based approach was used to collect additional inputs from individual regulatory authorities, with the objective of i) challenging the regional regulatory system by expanding the pool of samples, ii) verifying that the same regulatory practices are in fact adopted by all member states, and iii) confirming the same level of performance is achieved by all member states, in all functions and in both product streams.

2.4. With no exception, all National Competent Authorities in 30 individual member states of the network were requested to provide documented evidence of implementation of one or more indicators. , **PROGRAMME OF PERFORMANCE**

EVALUATION

The performance evaluation was conducted over the period from February 9th, 2024, to April 15th, 2024, according to the calendar of activities outlined below, which was discussed and agreed with EMRN

PE activity	Date (please, indicate dates of specific PE activities and NA in case PE activity was not conducted)	Onsite/offsite (please, indicate if the activity was conducted face-to-face or remotely)
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Abridged tool	02/02- 15/04/2024	Desk based review of self-assessment (remote assessment)
Interviews with RA representatives	04/04/2024; 12/04/24; 15/04/24	Virtual meetings, remote assessment of additional evidence

3. PERFORMANCE EVALUATION PROCESS

3.1. GBT ML3 and ML4 mandatory sub-indicators

Pre-selected GBT sub-indicators were analyzed through a WHO desk-based review of the self-assessment provided by the EMRN.

As foreseen by the abridged evaluation pathway (see Annex 6 of the PE manual), 45 out of 268 pre-selected GBT sub-indicators have been subject to desk-based WHO assessment, 29 of them being associated with ML3 and 16 with ML4 (*Note: all ML4 included in the assessment were mandatory for WLA*).

All sub-indicators in the abridged tool are considered applicable and relevant for listing; therefore, even in the case of “for information only” GBT sub-indicators (21 sub-indicators out of 45), additional information was requested whenever considered necessary to acquire a full picture of the regulatory practices in place.

All GBT sub-indicators were satisfactorily met by the EMRN (EMA and all NCAs) in the field of medicines [including multisource (generics) and new medicines (new chemical entities), biotherapeutics and similar biotherapeutic products], and vaccines.

3.2. PE indicators

PE indicators were analyzed through a WHO desk-based review of the self-assessment provided by the EU network, followed by interviews to clarify highlighted aspects.

As foreseen by the abridged evaluation pathway (see Annex 6 of the PE manual), all PE indicators have been subject to WHO assessment, as they are considered applicable and relevant for listing.

All PE indicators were found satisfactory in the EMRN in both product streams.

3.3. PE tool for MA

NA

3.4. PE tool for VL

NA

3.5. PE tool for RI

NA

3.6. PE tool for LT

NA

3.7. PE tool for CT

NA

4. OUTCOME OF THE PERFORMANCE EVALUATION

4.1 Best practices, as applicable

The EU/EEA network was confirmed to act as an extremely mature regulatory system, aligned with Good Regulatory Practices, well structured, effective and subject to continuous improvement, whose regulatory decisions are reliable, scientifically supported, rigorous and transparently communicated to a variety of stakeholders, including the public.

The complexity of such a big regional system, composed of so numerous separate institutions in as many different countries, that could represent an obstacle to the implementation of harmonized regulatory practices, has been in fact converted into a powerful asset, where diverse and multidisciplinary competencies are generously shared among all member states, to bring the same level of regulatory oversight across the entire network, ultimately leading to increased access to quality assured, safe and effective medical products, not only in the European region, but even beyond, due to the transparent approach used in sharing most of the regulatory processes and decisions.

Several best practices have been identified during the evaluation, the following deserving a special mention:

- a) **Common legal framework:** the presence of a robust common legal framework, in addition to the common regulatory framework, ensures all member states abide the same principles and apply the same regulatory approaches, thus setting the foundation for an effective regional regulatory body, which can successfully act as a single entity.
- b) **Reliance:** wide adoption of the concept of reliance in the entire region and robust networking are key for i) streamlining regulatory processes, ii) widening the areas of expertise of the regulatory body, iii) building new competencies, iv) benefitting from diversities (e.g., health needs depending on different populations and conditions), and v) contributing to health equity, in that all member states can have similar access to quality medicines.
- c) **Patients engagement:** Patients, consumers and carers are actively involved in a wide range of European Medicines Agency (EMA) activities, either as representatives of European Union (EU) patients' and consumers' organizations, representatives of their own organization or as individual experts depending on the nature of the activity, and can be involved in many aspects of the regulatory lifecycle of a medicine, from pre-submission and evaluation to post-authorization.
At the same time, such patients' participation is strictly regulated to avoid any type of conflict of interest and ensure impartiality and confidentiality; a specific training program is developed to ensure patients can substantially and significantly contribute to the decision-making processes.
This pioneering approach, where patients are members of EMA committees, is in place since 2000 and is under constant evolution.
- d) **Transparency:** the Agency strives to be as open as possible about how it works and how it comes to its decisions. To this end, EMA releases information on medicines

and manufacturers at various stages, during the entire lifecycle of a medicinal product. Positive and negative decisions, as well as grounds for such decisions, are timely communicated to the public. In addition, the presence of common databases across the network, ensures the majority of information is made available by all Member States and kept duly updated. The EMA has a policy of sharing assessment reports with international regulatory partners, while respecting the protection of personal data and other non-public information as required.

- e) **Trust building:** through the above-mentioned patients' engagement and transparency, the EU/EEA regulatory network continuously contributes to building citizens' and stakeholder's trust in the regulatory decisions and actions taken by this Regional Regulatory System.
- f) **Supporting research and innovation:** a range of services is available from the European Commission, Heads of Medicines Agencies (HMA), the European Medicines Agency (EMA), and the European Directorate for the Quality of Medicines (EDQM) to support innovative medicines and associated technology developments in the European Union (EU), including scientific and regulatory advices, initiatives to accelerate and improve innovation, identification of key innovation topics on which to build the competence and to foster open and constructive discussions with relevant stakeholders.
- g) **Enhancing global health:** with the introduction of article 58, since 2004 EMA helps addressing public health challenges in low and middle income countries (LMICs), by providing a mechanism through which scientific and manufacturing expertise is provided to manufacturers, WHO, NRAs from LMICs, and the broader global health community regarding development and assessment of products intended to be marketed outside EU/EEA. In addition, EMA is a leading regulatory partner supporting the WHO Collaborative Registration Procedure using stringent regulatory authorities' medicine evaluation (CRP-SRA), as well as the prequalification programme.

5. CONCLUSIONS

Following the abridged performance evaluation pathway, the EU/EEA network demonstrated to comply with all requirements set for a regulatory authority to be designated as WHO-listed authority in both product streams of medicines [including multisource (generics) and new medicines (new chemical entities), biotherapeutics and similar biotherapeutic products] and vaccines, as all pre-selected GBT sub-indicators and PE indicators in the abridged tool were satisfactorily met, not only by the regional authority (i.e., EC, EMA), but also by all individual regulatory authorities in all EU/EEA member states.

6. TAG-WLA REVIEW OF THE PERFORMANCE EVALUATION RESULTS AND RECOMMENDATIONS

The WHO secretariat presented findings of the PE, as outlined in the preceding sections, to TAG-WLA during the meeting held on 16-17 April 2024, in Geneva, Switzerland.

EMRN representatives were invited as observers to the open session of the TAG meeting on 17 April, to present their Regional Regulatory System and the activities conducted during the performance evaluation.

Based on the performance evaluation results presented and discussed during the meeting, the TAG-WLA recommended listing as WLA the European Medicines Regulatory Network (comprised of EC/EMA and the NCAs in 30 Member States mentioned above), as follows:

- A. **Vaccines**, for the following regulatory functions under the overarching regulatory system (RS):
 - 1) registration and marketing authorization (MA); (2) vigilance (VL); (3) market surveillance and control (MC); (4) licensing establishments (LI); (5) good manufacturing practices (GMP), good storage and distribution practices (GSDP) and good clinical practices (GCP) regulatory inspections (RI); (6) laboratory testing (LT); (7) clinical trials oversight (CT); and (8) NRA lot release

- B. **Medicines** (including generics and new medicines, biotherapeutics and similar biotherapeutic products), for the following regulatory functions under the overarching regulatory system (RS):
 - 1) registration and marketing authorization (MA); (2) vigilance (VL); (3) market surveillance and control (MC); (4) licensing establishments (LI); (5) good manufacturing practices (GMP), good storage and distribution practices (GSDP) and good clinical practices (GCP) regulatory inspections (RI); (6) laboratory testing (LT); and (7) clinical trials oversight (CT).

The TAG further recommends that an explanatory note should be provided about the common process and evaluation adopted for the assessment of individual NCAs.

