Regulatory collaboration

Collaboration, not competition: developing new reliance models

Exchange of assessment reports (ARs) with regulators outside the European Union (EU)\(^1\)

At a time when modern medicines manufacture and distribution are increasingly globalized, cooperation between medicine regulators has become essential, and multiple models of regulatory collaboration are being implemented in all regions of the world. The European regulatory system for medicines is unique in the global regulatory environment and may serve as a model for other countries or regions for building trust and mutual reliance. The EU Medicines Agencies Network Strategy to 2020 highlights the strong international role that the EU network can play in promoting reliance and work-sharing with other regulators.

This paper provides a discussion of the programmes and initiatives in which medicines regulators rely on collaboration and on assessment work carried out by other regulators while retaining responsibility for their own regulatory decisions. It also proposes some tools and suggestions to make these approaches more systematic. The paper concentrates on assessment of applications for marketing authorization, but many concepts expressed here can be applied to other regulatory areas such as inspections and pharmacovigilance.

Although the focus is on exchange of documents produced by the European Medicines Agency (EMA) and other agencies in the EU network with regulators outside the EU, it is recognized that the EU regulatory system also has much to gain by exchanging experience with, and receiving information from, regulators in other regions of the world.

\(^1\) The 28 EU Member States plus Iceland, Liechtenstein and Norway form the European Economic Area (EEA). Most of the EU rules, procedures and practices described in this article apply to all the EEA countries.

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Any feedback on ways to achieve or improve cooperation would be very much appreciated by the EMA and the other agencies in the EU network, and can be addressed to EMA through the mailbox: emainternational@ema.europa.eu.
Introduction

Current regulatory challenges
Modern medicines manufacture and distribution are becoming more and more globalized. As a consequence, the manufacturing processes and supply chains of pharmaceutical products, including generics, are increasingly complex. The same medicinal product is often distributed in several countries or world regions and used by patients all over the world. It is also common that different manufacturing phases for the same product take place in different countries, often very far away from each other. At the same time, more and more common elements are present in the dossiers submitted in different jurisdictions.

In addition, new medicines coming to the market are often complex products such as biotechnology, gene therapy or cell therapy products, or have sophisticated formulations involving e.g. micellar systems or nanoparticles. Some regulators may lack the resources or specific competences to carry out assessments of these products before they are put on their markets.

In this environment, collaboration among regulators is essential to avoid duplication of work, release scarce resources for more critical areas and speed up patients access to new and/or affordable products.

New models of cooperation
The growing awareness of the need for regulators to work together has led to the emergence of new models of cooperation. The European medicines system is probably the best-established example of regulatory cooperation between medicines authorities, with a legal basis dating from 1965. It has a long history of developing effective cooperation within Europe and may serve as a model for other countries or regions for building trust and mutual reliance. The EU Medicines Agencies Network Strategy to 2020 (1), published in December 2015, highlights collaboration in the global regulatory environment as a strategic priority area and aims at further developing a strong international role for the network by, among other things, capacity building and promoting reliance and work-sharing with other regulators.

A number of other countries and regions have also developed or are developing formal and informal frameworks for cooperation and work-sharing, helping avoid duplication and use resources efficiently. A few examples are given below; the list is far from being exhaustive.

In the Region of the Americas, which comprises 55 countries, the Pan American Network for Drug Regulatory Harmonization (PANDRH) is a forum of national medicine regulatory agencies whose aim is to promote regulatory harmonization between them, including technical guidelines and regulatory processes, while the Caribbean Community (CARICOM) is advancing a project to develop a regional regulatory system.

In Africa, several regional communities and projects are in place to develop cooperation mechanisms, such as the East African Community (EAC) and the Southern African Development Community (SADC), which are working towards harmonization among the participating authorities, and the ZaZiBoNa project, which connects the regulatory systems of the four participating countries (Zambia, Zimbabwe, Botswana and Namibia) with a view to expanding the project to other countries. The African
Vaccine Regulatory Forum (AVAREF) is developing mechanisms and pathways for expedited regulatory review of clinical trials for products being developed to address public health emergencies and neglected diseases, including joint review by regulators and ethics committees. A timeline for the establishment of an African Medicines Agency has been recently established (2).

The Association of Southeast Asian Nations (ASEAN), the Asia-Pacific Economic Cooperation (APEC) and the Gulf Central Committee for Drug Registration (GCC-DR) are among the regional initiatives in Asia working towards harmonization for medicinal products.

Collaboration and reliance
Regulatory collaboration can be achieved in a variety of ways, including information and/or work-sharing and mutual recognition of assessment and inspection results.

Forms of cooperation such as mutual recognition agreements, which require establishment of a strong legal framework, are desirable and should be implemented whenever possible. However, they take a long time to set up, as the regulatory systems involved need to be mutually assessed and shown to be equivalent before implementation.

An alternative way to achieve cooperation and avoid duplication of work is what is often referred to as reliance. Reliance is a broad concept and can be achieved in real life in different ways. In general, reliance implies that the work done is shared by the trusted authority (e.g. through assessment or inspection reports), while the receiving authority uses this work according to its own scientific knowledge and regulatory procedures and retains its own regulatory responsibilities. For example when an assessment report for a medicine authorized in the EU is shared with a regulatory authority in Africa, the receiving authority might still need to consider differences in conditions of use, patient population and other parameters.

In many cases reliance on the assessment or inspection work carried out by another trusted regulatory authority can be the best way to cooperate effectively. Reliance can be unilateral, bilateral (mutual) or multilateral.

EU registration pathways
The EU regulatory model has evolved significantly over time, particularly since the creation of the European Medicines Agency (EMA), the Centralised Procedure and the Mutual Recognition Procedure in 1995. The various routes to medicines approval in the EU system (Table 1) are

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<th>Route</th>
<th>Description</th>
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<td>Centralised Procedure (CP)</td>
<td>Assessment via EMA, resulting in a single marketing authorization throughout the EU</td>
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<tr>
<td>Decentralised Procedure (DCP)</td>
<td>Assessment of a new (not previously authorized) medicine by a Reference Member State on behalf of a group of other Member States</td>
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<tr>
<td>Mutual Recognition Procedure (MRP)</td>
<td>Assessment of a medicine authorized in at least one Member State by a Reference Member State on behalf of a group of other Member States</td>
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<tr>
<td>National procedures</td>
<td>Assessment by a Member State of a medicine for approval in its own jurisdiction</td>
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based on a single assessment system so that any assessment report (AR) from any of the agencies in the EU network can be used as a basis for reliance by other regulators.

Exchange of complete, unredacted ARs plays an important role in regulatory cooperation. EU regulators share their unredacted ARs with regulators outside the EU in several established initiatives and other contexts, as described below. This exchange is often based on confidentiality agreements, but in the spirit of regulatory collaboration ARs can also be exchanged where there is no such agreement in place and the applicant for marketing authorization consents to this sharing. This allows the extensive assessment work carried out by EU experts to be used by other international regulators for the benefit of patients. The different means used to achieve such sharing of ARs in practice are explained later in this paper.

Information-sharing initiatives involving EU ARs

**IGDRP information-sharing pilots with EU’s Decentralised and Centralised Procedures**

The information-sharing pilot of the International Generic Drug Regulators Programme (IGDRP)\(^2\) was launched in July 2014 using the EU Decentralised Procedure (DCP) as a model for cooperation. It provides a mechanism for sharing of information during the scientific assessment phases of the procedure. During Decentralised Procedures for generics participating in the pilot, ARs are shared by the EU agencies in real time with the participating non-EU authorities, upon request from the company applying for marketing authorization. The receiving authorities benefit from the information in the EU ARs but maintain their own regulatory responsibilities for decision-making.

Currently the pilot involves EU authorities as well as Health Canada, Swissmedic, the Taiwan Food and Drug Administration (TFDA) and the Therapeutic Goods Administration (TGA) of Australia. Other members of the IGDRP may decide to take part at a later stage.

In January 2015, the information-sharing pilot was extended to include applications for generics submitted through the Centralised Procedure, allowing EMA to share its ARs relating to these submissions with the collaborating non-EU regulatory agencies in real time.

The EU is leading this initiative with the aim of strengthening the scientific assessment, increasing consistency in the assessment of generics and saving global assessment resources.

**WHO collaborative registration pilot for stringently authorized products, including through the EU’s Article 58 Procedure**

The World Health Organization (WHO) collaborative registration pilot for medicines approved by a stringent regulatory authority (SRA)\(^3\) was initiated in 2015 as an extension of a WHO procedure that facilitates and accelerates the national registration of products already assessed and prequalified by WHO. The pilot aims at facilitating the registration of SRA-approved essential medicines in countries where regulatory

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2  https://www.iggrp.com/

3  Defined in WHO guidance (3) as a regulatory authority in a country that is a member of the International Conference on Harmonisation (ICH) or an ICH observer country, or a regulatory authority associated with an ICH country through a legally binding mutual recognition agreement
resources may be limited. Here as well, the receiving competent authorities retain their regulatory responsibilities and make their own decisions.4

Since November 2014 EMA has participated in the development and implementation of the pilot. In this context, EMA ARs are shared with regulators in African countries by companies holding EU marketing authorizations who wish to market their products in these countries. EMA confirms, upon request from the company, that it has no objections to the sharing of its ARs and, in accordance with WHO procedures, confirms that the Quality Information Summary provided by the company complies with the information in the dossier assessed by EMA. EMA can provide the receiving authority with further information or clarification on any aspect of the assessment and promotes dialogue between the receiving authority and the relevant EMA assessors as required.

At the time of writing, EMA participation has involved three Centrally Authorized Products and one assessed under Article 58 (see below), for the treatment of HIV, malaria or tuberculosis.

Article 58 of Regulation (EC) No. 726/2004 (4) allows EMA’s Committee for Medicinal Products for Human Use (CHMP) to give opinions, in co-operation with the WHO, on medicinal products for human use that are intended exclusively for markets outside the EU. This includes vaccines used in the WHO Expanded Programme on Immunization, medicines used to treat public health priority diseases, and medicines for WHO target diseases such as HIV/AIDS, malaria or tuberculosis. Under Article 58 the CHMP carries out a scientific assessment according to the same standards as it would for Centrally Authorised Products authorized for marketing in Europe, taking into account possible different conditions of use. Experts and observers from WHO or from WHO Member States (appointed by WHO) are part of the assessment process. The CHMP, after consultation with WHO, adopts a scientific opinion, following the process in place for the Centralised Procedure.5

An Article 58 Procedure followed by collaborative registration provides a useful approach to speeding up patient access to essential medicines, including new or improved therapies for unmet medical needs, without compromising on the quality of assessment.

Other uses of EU assessment reports by non-EU regulators

Non-EU regulators often request applicants to provide EU ARs in contexts other than the information-sharing initiatives described above. The use of EU ARs in the receiving country may be included in the legislation, guidelines or procedures of these countries. Some examples are given below.

Switzerland

The Swiss legislation (5) foresees that for a medicinal product which has already been granted an authorization in a country with a comparable control system for medicinal products, the assessment by the reference authority will be taken into account by Swissmedic during the authorization procedure, provided that the applicant explicitly requests Swissmedic to do so. The goal is to make medicinal products already authorized in

4 More information is available at http://apps.who.int/prequal/ under “Collaborative Registration”.

foreign countries available to patients in Switzerland as rapidly as possible while ensuring a targeted, risk-assessed use of Swissmedic’s resources.

Use of an existing EU AR in this way has decreased the review time by up to about 20%. In 2015, about 15% of medicinal products with known active substances authorized in Switzerland were authorized taking into account ARs produced by EMA or an EU Reference Member State. In addition, there are products for which the approval decision is not based solely on shared EU reports. Applicants are encouraged to always submit any such ARs as they are considered a valuable source of information.

**Canada**
In Canada, a draft guideline was published in 2012 (6) which details how information submitted by applicants on reviews carried out by foreign authorities can be used by Health Canada during the assessment of applications. The guideline recognizes that the Canadian law does not prevent Health Canada from using, where appropriate, foreign reviews to perform part of the evaluation or to inform Health Canada’s decision-making. Health Canada however cannot grant (or refuse to grant) marketing authorization based solely on the existence of a foreign review and its corresponding regulatory decision.

Different levels of reliance on foreign reviews are detailed in the guideline, allowing for the possibility that a critical assessment of the foreign review is used as a basis for the Canadian regulatory decision on the entire data package or on one or more of its components.

**Singapore**
Legislation in Singapore (7) allows for leveraging of foreign reports to grant marketing authorizations. The reference agencies accepted by the Singapore Health Sciences Authority (HSA) are EMA, U.S. FDA, Health Canada, TGA and MHRA (for national products or Decentralised and Mutual Recognition products where MHRA is the Reference Member State). For applications that have obtained prior approval from these reference agencies, HSA has a system that enables leveraging of assessments performed by these agencies, called the Verification Route (VR). To be eligible for the VR, one of the criteria is that the product is authorized for marketing in any two of the HSA’s reference agencies.

The VR takes 60 days (excluding clock-stops) as opposed to the 270 days necessary for products not previously authorized by any other authority (Full Route) or to the 180 days for products authorized by at least one drug regulatory authority (Abridged Route). 5% of the products authorized in Singapore in 2015 have been authorized via the VR using EMA assessment reports.7

**Mexico**
In 2012, EMA was approached by the Mexican medicines regulator COFEPRIS to facilitate an assessment of legal equivalence between the Mexican and EU pharmaceutical legislation. After dialogue with EMA lawyers, the result was a unilateral agreement (“acuerdo”) (8) through which Mexico uses the work carried out at EMA during assessment of Centrally Authorised Products to expedite approval of new medicines in Mexico. Similar arrangements are in place between Mexico and some other

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6 Personal communication received from Swissmedic

7 Personal communication received from HSA
countries, including the United States, Canada, Australia and Switzerland.

**Modalities for exchange of information with non-EU regulators**

**Sharing of assessment reports (ARs)**

EMA ARs (for both the Centralised and the Article 58 procedures) and ARs from other agencies in the EU network are shared with non-EU regulators directly or through the marketing authorization holder.

Although EU ARs include commercially confidential information, they can be exchanged by EMA and the other agencies in the EU network with other regulators when there is a Confidentiality Arrangement in place between the EU and the receiving authority. Through these arrangements the parties agree not to disclose confidential information.

In the absence of such an agreement, unredacted EU ARs can still be exchanged directly with non-EU regulators, provided that the marketing authorization holder for the products consents to the exchange. EMA is encouraging such direct exchanges as far as possible, and a template to be used by companies to consent to exchange of ARs has been made public on the EMA website. EU ARs can also be provided by EU authorities without consent from the marketing authorization holder, but in these cases confidential information is redacted.

When marketing authorization holders are requested by a non-EU authority to share EU ARs for their products, they may ask the relevant EU agency to confirm in writing that it has no objection to the sharing. Unless there are serious reasons to object, the EU agency indicates to the company concerned that it does not object. A standard wording for responding to such requests has been developed and published on the EMA website.

**Public ARs**

Notwithstanding the measures identified above the EU assessment process is exceptionally transparent, and the possibility of taking advantage of what is made public on the websites of EMA and the other agencies in the EU network should not be underestimated. The EMA website, for example, is continuously updated with information on the quality, safety and efficacy of Centrally Authorised Products. For every medicine, including those with a positive opinion under Article 58, a European Public Assessment Report (EPAR) is published, which gives a wealth of information on the product, its use and its assessment. EMA also publishes information on medicines which receive a negative opinion from the CHMP.

Similar public ARs are published by other agencies in the European network. Public ARs for products assessed through the Mutual Recognition Procedure are published in the MR Product Index on the Heads of Medicines Agencies website.

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8 Confidentiality Arrangements are in place between the EU and the following organizations: US Food and Drug Administration (FDA); Health Canada (HC); Japan Ministry of Health, Labour and Welfare (MHLW) and Pharmaceutical and Medical Devices Agency (PMDA); Swissmedic; Australia Therapeutic Goods Administration (TGA); World Health Organization (WHO)

9 Available in the EMA questions and answers on pre-submission guidance, Question No. 68 at: www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000157.jsp

10 More information on EPARs is available at: www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d125

11 Available at: www.hma.eu/mriproductindex.html
Additional approaches
Exchange or publication of ARs are not the only ways in which cooperation on medicine assessment among regulators can be achieved or information on assessment can be exchanged. Other possibilities are being explored, such as allowing regulators from other jurisdictions to listen to, or participate in, relevant product-specific meetings and discussions. The possibility of post-authorization webinars, where the scientific rationale for the decisions taken by an agency is explained and discussed with other regulators, may also be considered.

Remaining barriers
There are still barriers to overcome in furthering the exchange of assessment and inspection information among regulators worldwide. Such barriers can be legal (e.g. lack of legal framework, confidentiality issues), technical (e.g. lack of secure IT platforms for information-sharing), and non-technical (e.g. political issues, lack of trust). However, none of them should be big enough to prevent cooperation and sharing of information among regulators, given the benefits it can bring to patients worldwide.

EMA and the other agencies in the EU network are committed to finding ways to overcome such barriers wherever they exist. For example, in the absence of a globally accepted secure IT platform, they share unredacted ARs through the EU secure email system, Eudralink, which is encrypted and password-protected. Multilateral cooperation forums such as WHO groups and committees, the International Conference of Drugs Regulatory Authorities (ICDRA), the International Coalition of Medicines Regulatory Agencies (ICMRA), the Pharmaceutical Inspection Co-operation Scheme (PIC/S) and the International Generic Drug Regulators Programme (IGDRP) among others provide excellent platforms for working together to overcome remaining difficulties.

Conclusion
The challenges faced by regulators in an increasingly complex regulatory environment are shared and recognized by the EU agencies network, and the need for cooperation is emphasized in the recently published EU network strategy (1). EMA and the other agencies in the EU network are willing to provide support and to cooperate with other international regulators as much as possible, while at the same time benefiting from the work done by other authorities as far as possible.

As demonstrated by examples from other regions of the world, the EU authorities are not alone in favouring and promoting sharing of ARs and other regulatory documents (e.g. inspection reports). However, such cooperation is currently mainly carried out at regional level. It makes little sense that the work carried out by regulators in one part of the world is not shared with regulators in other regions. The cooperation and sharing need to be more global in order to be more effective.

It has become increasingly clear that forms of cooperation requiring a strong legal framework often require a very long time to be achieved. An alternative approach is that of reliance, in which regulatory authorities make use of shared information but retain their decision-making responsibilities. Reliance can be unilateral, bilateral or multilateral, can be achieved in a short timeframe, does not require a heavy legal framework, and can
be the prelude to more formalized forms of cooperation such as mutual recognition agreements.

To promote reliance and work-sharing in line with the EU network strategy to 2020, EMA and the other agencies in the EU network will continue to share unredacted EU assessment and inspection reports with other regulators worldwide as much as possible, and will actively develop new and better ways to facilitate cooperation and exchange of information to realize the greatest possible benefits for patients.

References

1 EMA. EU Medicines Agencies Network Strategy to 2020. Working together to improve health. London: European Medicines Agency; 17 December 2015. Available at:

2 AMRH. 2nd Task Team meeting to facilitate the establishment of African Medicines Agency (AMA) successful. AMRH Newsletter January–June 2016; pp. 5-6.


5 Swiss Confederation. Federal Act on Medicinal Products and Medical Devices (Therapeutic Products Act, TPA) of 15 December 2000. Article 13, Medicinal products authorised in foreign countries, and Ordinance of 17 October 2001 concerning Medicinal Products (Medicinal Products Ordinance), Articles 5a - 5d.


7 Health Sciences Authority (HSA). Guidance on medicinal product registration in Singapore. Effective 1 April 2011.