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# How Int'l Regulatory Collabs Can Expedite Pharma Approvals

By **Geneviève Michaux and Christina Markus** (October 23, 2023, 6:09 PM EDT)


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The U.K. recently announced that, beginning in 2024, it will authorize the marketing of drug products through recognition of foreign approvals.

In 2020, several national medicines agencies collaborated through the International Coalition of Medicines Regulatory Authorities to accelerate the approval of COVID-19 vaccines.

In 2019, the U.S. Food and Drug Administration launched Project Orbis, enabling the review of drug applications in collaboration with other national health regulators. These events illustrate the growing importance of international regulatory collaboration for drug approval, both in emergency and nonemergency situations.

International regulatory collaboration takes many forms, especially reliance and exchange of information. Reliance has already been recognized as a modern regulatory tool since it carries the potential to bring drugs to market faster and more efficiently.[1]

For the last 10 years, regional authorities and national regulators invested efforts in improving the efficiency of existing reliance processes, especially in Africa and the Middle East, and setting up new reliance-based regulatory models. Information exchange is a less demanding form of collaboration that nevertheless encourages or leads health regulators toward similar decisions.

Product sponsors may be unfamiliar with collaborations that may be useful to global marketing of their products. In addition, practical considerations are important, such as:

- The resources needed to prepare and prosecute multiple applications in different jurisdictions at once;
- Cost, e.g., application or annual fees may be due to multiple countries;
- Establishment of a corporate presence or agent in various countries;
- Commercial infrastructure, and pricing and reimbursement approvals in multiple countries; and

- Timing and its impacts, e.g., whether a product may qualify for a time-limited period of data exclusivity post-approval, the sponsor is prepared to launch, and the product will be first on the market.

This article describes key collaborations currently available to pharmaceutical companies. It assesses their actual efficiency and utility to pharmaceutical companies.

**Why Collaborations Are Needed**

Generally, drugs may be placed into a nation's market only after approval by the local, competent health regulator, considering scientific data from the sponsoring company.

However, national rules on approval procedure and requirements vary, and certain countries lack regulatory resources or expertise, which renders multicountry commercialization challenging and forces companies to sequence approvals and perhaps exclude certain countries. As a result, patients may not receive access, or receive delayed access, to novel drugs.

Some issues can be resolved through collaborations that typically seek to reduce the time from submission to approval, avoid duplication of efforts, and decrease workload and financial needs. Furthermore, collaborations contribute to capacity building in low- or middle-income countries and help those countries develop their own regulatory systems.

Collaborations take many forms.

"Reliance" is defined by the World Health Organization as the use of the work or decision of another national authority as an input for one's own regulatory procedure. This broad term thus covers recognition of foreign approvals, joint scientific assessments and reliance on other health regulators' assessments.

Mutual recognition agreements — typically covering manufacturing — and confidentiality agreements enabling data exchange among health regulators also are collaborations.

They have different scopes, both in terms of interactions among regulators — approvals, inspections, etc. — and products. Some collaborations cover all medicinal products, and others are restricted to specific drug categories such as drugs for unmet medical needs or infectious diseases.

**How Collaborations Can Be Successful**

Besides a political will, the success of collaborations depends on three factors.

First, rules and standards must be harmonized among collaborating countries, and confidentiality agreements must be in place to allow exchange of information. This explains why many collaborations involve countries in the International Conference for Harmonization of Technical Requirements for Pharmaceuticals for Human Use, for example, which has a long history of working to develop common standards.

Secondly, health regulators must learn to trust each other and their scientific assessments. Familiarity and trust need time and opportunities to build.

Therefore, companies must be willing to participate in collaborations. Once regulators have agreed on a collaboration, it falls on the potential users to take the collaboration to the next level by using it, thereby allowing regulators to build trust.

Then comes the user reality check to improve the actual functioning of the collaboration. In other words, companies participate in the success of collaborations by accepting their temporary lack of efficiency in the hope of fixing it for the best.

**From Recognition to Information Exchange**

Current collaborations rely on foreign approvals, joint scientific assessments, other health regulators' assessments and information exchange.

***Recognition of Foreign Approvals***

Several countries accept approving drugs based on approvals granted in another country or by a specific institution, be it after having carried out a few verifications, depending on country. This is the highest form of collaboration, although it does not require a formal agreement among countries but a law from the recognizing country.

The most well-known examples are Israel, and soon, the U.K. After Brexit, the U.K. Medicines Agency was able to rely on EU approvals to authorize drugs in Great Britain, through the European Commission Decision Reliance Procedure, to avoid significant deviations from EU approval pathways and duplication of efforts.

Beginning in 2024, the European Commission Decision Reliance Procedure will be replaced by an international recognition procedure whereby the Medicines and Health Care Products Regulatory Agency will take into account approvals granted by reference regulators: Australia, Canada, the EU, Japan, Switzerland, Singapore and the U.S.[2]

Many other countries also rely on foreign approvals. For example, most countries in Latin America and the Caribbean allow recognition of foreign approvals based on, or an abbreviated procedure in case of, prior approval in the U.S., the EU or Canada.

Overall, decisions taken by the U.S. Food and Drug Administration, European Medicines Agency or Health Canada are fully recognized in about two-thirds of Latin American and Caribbean countries.

***Joint or Common Approval Procedure***

Certain countries have agreed to collaborate in scientific assessments while keeping their decision-making power or delegating it to a higher, regional authority.

*European Union (EU)[3] - Approval Procedures Under EU Pharmaceutical Law*

The 27 EU member states collaborate through two main procedures.

In the case of a centralized procedure, the sponsor submits a single application to the European Medicines Agency, or EMA, which assesses the data package The European Commission then grants a single approval for the entire EU. The Committee for Medicinal Products for Human Use, the EMA's

main scientific body entrusted with scientific assessments, includes representatives of each EU member state.

In the case of a decentralized procedure, the sponsor submits its application to each EU member state where it wants to market the drug, but the scientific assessment is conducted jointly by national health regulators. Each member state decides on the application and grants its own, national approval.

*Access Consortium (Australia, Canada, Singapore, Switzerland, U.K.)*

The consortium promotes regulatory information and work sharing initiatives relating to new active substances, biosimilars and generics.

The New Active Substances Work-Sharing Initiative focuses on innovative drugs with extensive data packages. A presubmission meeting with all participating countries leads to a consolidated roadmap for review, including dates. The company submits an application in each country, and regulators provide priority review status under national law.

The authorization dossier is divided for review among the countries, and the company receives a consolidated list of questions. Each country independently decides on the application.

*African Regulatory Harmonization Programs — Decentralized Procedures*

Three programs have been launched under the African Medicines Regulatory Harmonization, each of which covers a different regional economic community and includes harmonization of rules and a decentralized procedure:

- East African Community Medicines Regulatory Harmonization Program;
- West African Medicines Regulatory Harmonization Program; and
- ZaZiBoNa Collaborative Procedure for Medicines Registration.

The review processes include one application dossier and a same response package to the participating countries. The company thus accesses several African markets, within the same general time frame. In practice, however, the features and specific timelines differ among the three economic regions.

The collaborations have been fairly successful. However, improvements are needed such as more robust information technology systems, centralized submission and tracking systems, and increased information on submission processes.

*ASEAN Joint Assessment Procedure (Brunei, Cambodia, Indonesia, Laos, Malaysia, Myanmar, Philippines, Singapore, Thailand, and Vietnam)*

In 1999, the ASEAN Consultative Committee for Standards and Quality established the Pharmaceutical Product Working Group to harmonize pharmaceutical regulations across ASEAN member countries. The Pharmaceutical Product Working Group launched the Joint Assessment Coordination Group and a formal joint assessment procedure.

Participation in the procedure is open to all ASEAN member states, on a voluntary and product-by-

product basis. Under the joint assessment procedure, the same application is simultaneously submitted to all participating national regulators. The scientific assessment is conducted by all participating regulators and a joint assessment report is prepared. At the end of the process, each individual regulator takes a decision on the application but based on the joint report.

*Gulf Health Council (Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, United Arab Emirates, Yemen)*

The Gulf Centralized Committee for Drug Registration implements two drug approval procedures: (1) a centralized procedure carried out by the executive office of the GCC-DR; and (2) a decentralized procedure that preserves national approval procedures of each country.

The centralized process has several levels. An abridged procedure applies where the drug has been approved by at least two Gulf Cooperation Council countries or by the FDA, EMA or WHO. In such cases, the GCC-DR only reviews local aspects.

In practice, the decentralized procedure is not used because the national regulatory procedures include price agreements, which make it easier to apply separately in each Gulf Cooperation Council country. Price agreements are no longer part of the centralized procedure but have to be addressed at the national level, after the centralized approval.

*Eurasian Economic Union*

The EAEU aimed at creating a common market for drugs and medical devices, which required harmonizing the rules and collaboration for drug approvals; hence, the EAEU member states agreed on a decentralized procedure[4] similar to the EU procedure.

Ninety-five percent of pharmaceutical regulations in the Eurasian market are aligned with EU and international standards, which should incentivize companies' use of this collaboration. Its operational implementation however is challenging due to regulatory complexities and difficulties with unifying the procedures. Some companies have used the decentralized procedure with success, but it is now on hold due to the Ukraine-Russia war.

***Reliance on Foreign Scientific Assessments***

Certain countries will base approval decisions on scientific assessments conducted by another health regulator.

*EU — EU Medicines for All*

EU-M4ALL, previously known as the Article 58 Procedure, is a procedure whereby the EMA, in cooperation with the WHO and non-EU health regulators, provides scientific opinions on high-priority drugs intended for non-EU markets.

The objective is to facilitate patient access to certain drugs in low- and middle-income countries. The eligible products are drugs, especially vaccines, used to prevent or treat public health priority diseases.

Although the EU-M4ALL procedure has potential to accelerate global access to key drugs around the world, only 12 EMA scientific opinions have been issued in about 20 years, which shows that improvement is needed.

*Switzerland — Marketing Authorization for Global Health Products Procedure*

The MAGHP procedure seeks to improve access to drugs by strengthening regulatory systems in low- and middle-income countries. The Swiss approval and scientific advice procedures are accessible to regulators in low- and middle-income countries and the WHO.

The procedure follows the Swiss standard approval procedure, but foreign health regulators and the WHO are invited to participate actively in the scientific assessment, with the aim of building their capabilities and establishing confidence in the process, while also accelerating approval in their countries.

Ultimately, the decision of Swissmedic, the Swiss surveillance authority for medicines and medical devices, is sent to the participating foreign health regulators who then have a 90-day period to decide on the application.

*WHO — Collaborative Registration Procedure Using Stringent Regulatory Authorities*

The SRA CRP allows national health regulators to have access to the work performed by so-called stringent regulatory authorities, i.e., their scientific assessment reports and inspection reports, to decide on drug approvals within their own jurisdiction. Simultaneous applications are submitted to the health regulators for the same drug as approved by the SRA, and they must decide within 90 days.

The current stringent regulatory authorities are the FDA, EMA, Health Canada, Swissmedic, Australia's Therapeutic Goods Administration, Japan's Pharmaceuticals and Medical Devices Agency, and the WHO.

***Exchange of Information***

Certain international collaborations simply organize an exchange of information among health regulators during scientific assessments.

*Project Orbis (U.S., Australia, Brazil, Canada, Israel, Singapore, Switzerland, U.K.)*

The FDA launched Project Orbis to facilitate concurrent application submission and review of clinically impactful cancer drugs and biologics.

Under Project Orbis, each country reviews a drug under its own application, laws and timelines, but the FDA coordinates the international outreach, participating regulators have regularly scheduled conference calls concerning their review, and they share information requests to minimize duplication.

Project Orbis already led to the approval of several life-saving drugs and biologics for patients suffering from various cancers. From June 2019 to June 2020, 60 applications were received, resulting in 38 approvals. It may also be used for supplemental applications.

In June this year, the European Union's EMA announced that it will become an observer to Project Orbis.

*Project OPEN (EMA, Australia, Canada, Switzerland, WHO and JPMA)*

Project OPEN seeks to allow international participation in scientific assessment, leveraging the existence

of confidential arrangements among the countries. EMA conducts a full review of the application but shares and discusses its assessment with a broader range of experts who, however, do not contribute to EMA's scientific opinion.

For now, only COVID vaccines and treatments have been examined under the framework of OPEN, but it will expand to antimicrobial resistance drugs, drugs designated under the PRIME scheme, drugs addressing unmet need, e.g., Alzheimer's disease, and drugs responding to health threats or public health emergencies.

***Regional Agencies***

Collaboration also occurs through the creation of regional medicines agencies whose general objective is to promote health in the region, which typically requires some level of harmonization and collaboration among the countries of that region.

The most recent examples are the African Medicines Agency that was created by a treaty that came into force on Nov. 5, 2021, and the Arab Drug Agency, the creation of which was formally accepted by the Council of Arab Ministers of Health in March. Those agencies are still in infancy but expected to follow the EMA model.

**Conclusion**

While many collaborations have been launched, very few are effective due to either a low binding effect or several factors such as lack of predictability of timeline, lack of administrative personnel and additional country-specific requirements.

Overall, even if a system does not yet operate optimally, the potential is there for companies to gain approval in several countries at the same time or based on a single assessment.

Collaborations run by International Conference for Harmonization of Technical Requirements for Pharmaceuticals for Human Use countries are currently more popular than other collaborations. Yet, those other collaborations carry great potential. Support from pharmaceutical companies would contribute to these collaborations meeting their objectives by creating necessary trust, and expertise of, the health regulators involved.

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[1] A. Saint-Raymond et al., Reliance is key to effective access and oversight of medical products in case of public health emergencies. Expert Rev Clin Pharmacol. 2022 Jul;15(7):805-810. doi: 10.1080/17512433.2022.2088503. Epub 2022 Aug 9. PMID: 35945703.

[2] MHRA, Guidance on International Recognition Procedure, Aug.30, 2023.

[3] The EU procedures extend to three EFTA States: Iceland, Liechtenstein, Norway.

[4] They also agreed on a mutual recognition procedure that is also very similar to the EU mutual recognition procedure.