Promoting the Quality of Medicines Plus (PQM+)

# PQM+ Support for Increasing Availability of Nirmatrelvir/Ritonavir and Molnupiravir to Treat COVID-19

## Results and Recommendations for Global Public Health Decision-Makers

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USAID FROM THE AMERICAN PEOPLE

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## About PQM+

The Promoting the Quality of Medicines Plus (PQM+) Program is a six-year cooperative agreement between USAID and USP to sustainably strengthen medical product quality assurance systems in low- and middle-income countries. The program works to improve medical product quality through cross-sectoral and systems strengthening approaches and the application of international quality assurance standards across the pharmaceutical system. By sharing scientific expertise and providing technical support and leadership, PQM+ helps create resilient and robust local health systems that address diseases such as HIV/AIDS, tuberculosis, malaria, and neglected tropical diseases, as well as improve maternal, newborn, and child health.

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## Suggested Citation



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# Contents

## Acronyms

| | |
|---|---|
| COVID-19 | coronavirus pandemic of 2019 |
| EUA | emergency use authorization |
| LMIC | low- or middle-income country |
| MoH | ministry of health |
| MPP | Medicines Patent Pool |
| NRA | National medicines regulatory agency or authority |
| NPV | net present value |
| PQ | prequalification |
| PQM+ | Promoting the Quality of Medicines Plus |
| SRA | stringent regulatory authority |
| T2T | test to treat |
| USAID | U.S. Agency for International Development |
| USP | U.S. Pharmacopeial Convention |
| WHO | World Health Organization |

## Background

In 2022, the U.S. Agency for International Development (USAID) invested $20 million from the American Rescue Plan Act to pilot a COVID-19 therapeutics test-to-treat strategy in 10 countries.[1] USAID sought to help countries prevent COVID-19 hospitalizations and deaths through timely diagnoses and access to oral COVID-19 antiviral medications.[2] USAID provided technical assistance to 10 countries to introduce and support scale-up of a COVID-19 T2T service delivery model using Paxlovid™ and Lagrevio™ and, eventually, their generic versions (nirmatrelvir/ritonavir [Nirmacom] and molnupiravir [Movfor], respectively).

To complement the service delivery activities, USAID asked the USAID-funded Promoting the Quality of Medicines Plus (PQM+) program, implemented by USP, to support increased availability of the medicines. PQM+ was asked to help:

- **Increase the supply** of nirmatrelvir/ritonavir by helping Medicine Patent Pool (MPP) sublicensees achieve World Health Organization (WHO) prequalification (PQ) for generic versions of Paxlovid™.
- **Increase the availability** of either antiviral medicine (nirmatrelvir/ritonavir or molnupiravir) in the 10 T2T pilot countries by helping their national medicines regulatory authorities (NRAs) authorize import and use of the product and by helping manufacturer(s) complete the authorization requirements in each country.

PQM+ worked to support authorization of the products from August 2022 through January 2024 and to support manufacturers towards attaining WHO PQ from August 2022 through March 2024.

## Increasing Supply

In November 2021, Pfizer and the MPP signed a license agreement to facilitate access to Pfizer's COVID-19 antiviral treatment Paxlovid™ (nirmatrelvir/ritonavir). MPP selected 35 manufacturers of generic pharmaceuticals to apply for sublicensee status so that they could pursue WHO PQ of their product and market it in any of the 95 countries designated in the agreement. USAID asked PQM+ to assist MPP sublicensees in obtaining WHO PQ as quickly as possible.

PQM+ sought to ascertain which of the 35 sublicensees were closest to achieving WHO PQ, what types of assistance could expedite achievement of PQ, and which companies were interested in receiving USAID-funded support to this end. PQM+ proposed supporting two companies based in South Asia and met with both manufacturers to clarify their needs. Ultimately, these experienced manufacturers did not require technical assistance. Rather, one of the most important limitations they both faced was a lack of some specialized equipment needed to process the nirmatrelvir and ritonavir active pharmaceutical ingredients (APIs). Given that manufacturers carefully weigh the investment they must make against likely sales when

[1] Bangladesh, Botswana, Côte d'Ivoire, El Salvador, Ghana, Lesotho, Malawi, Mozambique, Rwanda, and Senegal
[2] https://www.usaid.gov/news-information/press-releases/sep-23-2022-usaid-announces-countries-test-treat-and-oxygen-programming-COVID-19

deciding whether to pursue a new product, financial support in procuring this equipment was considered key to retaining their interest in developing nirmatrelvir/ritonavir and allowing them to reduce the cost of manufacture—and ultimately the price of the medicine. For these reasons, USAID agreed to share the cost of equipment (a roller compactor) with one manufacturer that was essential to producing the product and without which the manufacturer might have terminated their development of nirmatrelvir/ritonavir. Decisions about supporting procurement for these manufacturers were made on a case-by-case basis in close consultation with USAID.

PQM+ then helped the manufacturers source and vet qualified providers of the required equipment. In July 2023, the larger of the two supported manufacturers decided to cease its pursuit of WHO PQ for nirmatrelvir/ ritonavir because other companies were closer to WHO PQ and the company felt the remaining market did not justify further investment. The second manufacturer is still working toward WHO PQ for nirmatrelvir/ritonavir. This manufacturer required equipment to fully develop and commercialize its product and procurement of this equipment has taken time. This smaller manufacturer seeks to meet demand in its sizable national market (India) and export where possible.

The experience of attempting to provide meaningful support to manufacturers to reach this milestone yielded numerous lessons. It must be recognized that decisions of manufacturers, as for-profit businesses, will be highly affected by the market uncertainty, high level of risk, and other challenges facing pharmaceutical manufacturers in a global pandemic. This will limit many manufacturers' interests in pursuing WHO PQ or other authorization for a new medical product to be used during a pandemic. Those manufacturers with interest will constantly weigh rapidly evolving factors about patient demand, access to raw materials and consumables, and their competitive position.

Also, often large generic manufacturers in LMICs have little or no experience with donor support. They may not be interested in technical support that might divulge too much proprietary information to an outside consultant. They are likely to prioritize support that reduces their risk, most likely via an investment that defrays costs enough to impact their risk/benefit calculation.

From these and other lessons, PQM+ is able to offer recommendations for global public health decision makers (WHO and donors) on how best to increase supply of critical medical products in the next global pandemic. PQM+ offers recommendations for actions to take now and actions to be taken once an emergency is underway.

## Actions to take now

Global public health decision makers (e.g. donors and international organizations) should think now about strategies to increase sources of supply during a pandemic in order to be prepared for the next pandemic. What is the best way to attract manufacturers? How many sources are needed? What, if any, level of geographic diversity in suppliers is preferable? What types of support are likely to be preferred by manufacturers? How can this support be provided most efficiently and effectively? Among other things, global decision makers should consider how the strategy should be adjusted for different scenarios (e.g., if the pandemic were not subsiding, if the medicine were an established therapeutic rather than a new drug).

Donors that hope to support diversification of supply in future pandemics should maintain contacts and relationships with global generic pharmaceutical manufacturers and MPP to facilitate communication and collaboration in the event of an emergency.

A root-cause of delays in supporting the procurement of equipment for the supported manufacturer was the complexity and duration of federal procurement rules and procedures. Donors, implementing partners and other stakeholders involved in emergency response should also carefully review procurement rules and administrative procedures that introduced delay in this effort and determine whether they can be streamlined in readiness for future emergencies.

### Actions to be taken in an emergency

Donors and partners that seek to support diversification of supply should quickly establish contact with MPP to obtain early visibility into sublicensees. MPP should facilitate donor/partner contact with sublicensees to facilitate support.

Support for manufacturers should start early, ideally on release of the originator's technology package or sooner. Additionally, the entity providing support to the manufacturers should get early access to the technology package (with confidentiality adequately protected).

Plans for support should reflect realistic time frames and consider financial support to shift manufacturers' risk calculations.

## Accelerating Availability in the 10 Test-to-Treat Countries

PQM+ provided technical assistance to the 10 priority T2T countries to support the importation of COVID-19 therapeutics. PQM+ collected data on each country's regulations and processes for authorizing use of a new medicine. In many countries, PQM+ observed that transparency was lacking on pathways, requirements, criteria and conditions of approval, who made decisions, and timelines for decisions. It took significant effort and follow-up to obtain this information, which considerably slowed the process.

PQM+ also assisted manufacturers that had WHO prequalified COVID therapeutics with registering that product in T2T countries where submissions were not already completed. PQM+ also interfaced with regulators on behalf of manufacturers when there were delays in approval decisions.

Results of this support are summarized below.[3]

| Result | Movfor | Nirmacom |
|---|---|---|
| Approved | 4* | 3 |
| Application submitted, decision pending | 3 | 2 |
| Rejected | 1 | 0 |
| Approved but subsequently revoked | 1 | 0 |
| No application submitted | 0 | 4 |

[3] Note that, to protect local manufacturers, one of the T2T countries (Bangladesh) did not plan to approve any imported products (though it did issue import waivers in the interim). Accordingly, the status of applications and approvals is reported for only nine out of the 10 T2T countries in the table.

**In one case of approved Movfor, the market authorization certificate was not issued by the regulator, so the approval was not effective.*

While working to obtain approvals, PQM+ also supported USAID implementing partners and USAID Missions to obtain import waivers that allowed the product to be imported even though it was not duly authorized in the country. This is not the ideal mechanism for importation, as the regulatory review process is an important aspect to assuring medicine quality and to facilitating ongoing NRA oversight of the product and products are prone to stockouts once a waiver has expired. However, in the context of new drugs needed during an emergency, waivers may be an appropriate mechanism to ensure needed treatments are available to patients in a timely manner.

PQM+ identified two high-level themes that summarize the challenges faced in registering these new therapeutics in the T2T countries, specifically:

1. Perceived lack of scientific information to support therapeutic approvals in LMICs.
2. Lack of established and transparent emergency use authorization (EUA) or expedited pathways in LMICs.

Based on the experience gained and lessons learned, PQM+ recommends the following actions to ensure better preparedness for future COVID-19 outbreaks or other public health emergencies.

## Actions to take now

Medicines regulatory authorities (MRAs) should establish clear processes for EUA, reliance procedures, and other expedited review pathways now. MRAs should focus on adequate internal communication and dissemination of these processes and procedures, including through robust training programs, so that staff at all levels of the process are aware of the pathways and of their roles and responsibilities in facilitating the review of applications.

WHO and donors should continue efforts to support regional harmonization and reliance efforts. Regional regulatory harmonization initiatives will support legislation, guidelines, and procedures in countries within a region so that the regulatory authority in one jurisdiction can take into account and give significant weight to evaluations performed by another regulatory authority or trusted institution in reaching its own decision.[4] It takes considerable time to establish these harmonized regulatory frameworks and to build trust among authorities, so this work should start now.

WHO and donors should further educate Ministries of Health and NRAs in LMICs on the review processes used by stringent regulatory authorities (SRAs) and the WHO PQ process to increase trust in how these review processes assure the quality, safety, and efficacy of medical products. Regulators in LMICs need to understand the scientific rigor applied by SRAs and the WHO when approving new products, which will decrease perceptions that drugs are authorized without sufficient scientific data. This includes approvals or authorizations in response to an emergency, where a different threshold of supportive data is acceptable (i.e. lack of clinical studies conducted locally) to ensure access to life-saving treatments. Trust will reduce hesitancy

[4] Reference: https://cdn.who.int/media/docs/default-source/medicines/norms-and-standards/guidelines/inspections/grelp-annex-10-trs-1033/trs1033_annex10-good-reliance-practices.pdf?sfvrsn=dd5502cb_17&download=true

and help LMICs understand they do not need to duplicate processes and studies that SRAs have already completed.

Donors and supporting partners should establish and maintain relationships with the MoHs and NRAs prior to a public health emergency to build trust and enable pathways for communication about regulatory issues and concerns over a product's safety and efficacy.

## Actions to be taken in an emergency

During an emergency, WHO and donors should make available scientific and technical information on new products to NRAs in LMICs as quickly as possible. Developing official translations of key documentation into major languages will facilitate use of this documentation. Regulators in LMICs

Donors and other supporting partners can preemptively facilitate compilation of submission requirements, even while an SRA is reviewing a medical product dossier. This will help decrease the lag between medicine approval by an SRA and its subsequent approval and availability in LMICs.