

3rd Invitation to Manufacturers of therapeutics against COVID-19 to submit an Expression of Interest (EOI) for Product Evaluation to the WHO Prequalification Unit

To support national and global efforts to increase access to and affordability of products for treatment of COVID-19. WHO invites manufacturers of this pharmaceutical product to submit Expressions of Interest (EOI) for product evaluation.

ARTICLE 1. PROCEDURE FOR THIS INVITATION TO EOI

The current Invitation is published in accordance with the *Procedure for Prequalification of Pharmaceutical Products*, adopted in 2001 by the 37th WHO Expert Committee on Specifications for Pharmaceutical Preparations, and amended subsequently as part of the 45th report of the Committee, published as [No. 961 of the WHO Technical Report Series](#) in 2011.

Assessment of product(s) submitted under this Invitation will include evaluation of:

- product dossiers, which must include product data and information as specified in the guidelines for submission (see [Procedures & Fees](#))
- manufacturing sites, which must adhere to [good manufacturing practices](#) (GMP)
- clinical sites (if applicable), which must adhere to [good clinical practices](#) (GCP).

If evaluation demonstrates that a product and its corresponding manufacturing (and clinical) site(s) meet WHO recommended standards, it will be included in the list of medicinal products that are considered to be acceptable for procurement by UN organizations and others.

ARTICLE 2. MEDICINAL PRODUCTS INVITED

The aim of this Invitation is to increase the range of selected products and sources available in relation to management of the COVID-19 pandemic.

Dexamethasone

Dexamethasone, a corticosteroid, is included in the [WHO Model List of Essential Medicines, with clinical uses in multiple diseases and conditions](#), mainly as an anti-inflammatory agent. In COVID-19, a randomised controlled clinical trial (RECOVERY) has shown that dexamethasone reduced deaths by one-third in ventilated patients and by one fifth in other patients receiving supplemental oxygen compared to usual care alone. There was no benefit among those patients who did not require respiratory support

IL-6 Inhibitors

Tocilizumab and sarilumab are monoclonal antibodies that inhibit the Interleukin-6 (IL-6) receptor. Interleukin-6 is a cytokine produced by macrophages that induces a pro-inflammatory response. It is often elevated in patients with COVID-19.

Tocilizumab and sarilumab have been shown to provide benefit in hospitalized patients with severe or critical COVID-19. (Data supporting tocilizumab is more robust than for sarilumab.) They should be administered with

systemic corticosteroids. Tocilizumab and sarilumab are administered as single intravenous doses, typically over one hour.

Tocilizumab is dosed at 8 mg per kilogram of actual body weight, up to a maximum of 800 mg. Sarilumab may be dosed at 400 mg or 200 mg. Renal dose adjustment is not currently warranted for either drug.

Interested manufacturers are encouraged to submit documentation for recommended dosage forms as specified below:

Dexamethasone products¹:

1. Dexamethasone tablet, containing dexamethasone base 1.5mg, 2mg, 6mg
2. Dexamethasone oral solution, containing dexamethasone base 2mg/5ml or 10mg/5ml, as the base or sodium phosphate
3. Dexamethasone solution for injection, containing dexamethasone base 3.3mg/ml or 6.6mg/ml*, as the sodium phosphate
(*equivalent to dexamethasone phosphate 4mg/ml or 8mg/ml, respectively)

Tocilizumab products

Tocilizumab IV 20 mg/mL for further dilution prior to intravenous infusion.

Sarilumab products

Sarilumab 200 mg/1.14 mL for further dilution prior to intravenous infusion.

Sarilumab 150 mg/1.14 mL for further dilution prior to intravenous infusion.

For details on specific requirements for tocilizumab and sarilumab products, see:

[Prequalification Procedure \(PQ\) for Therapeutics: product specific requirements for currently invited therapeutics.](#)

ARTICLE 3. HOW TO SUBMIT AN EXPRESSION OF INTEREST

In order to submit an expression of interest for product evaluation, the manufacturer must send the requested documentation, arranged according to the information provided on the WHO Prequalification Unit – Medicines Assessment Team (PQT/MED) [website](#) in the [Procedures and Fees](#) section.

ARTICLE 4. QUALITY ASSESSMENT PROCEDURE FOLLOWING SUBMISSION OF AN EXPRESSION OF INTEREST BY A MANUFACTURER

The quality assessment is undertaken to evaluate whether the pharmaceutical product being evaluated meets the requirements recommended by WHO, and is manufactured in compliance with good manufacturing practices (GMP).

The procedure established by WHO for quality assessment incorporates:

- general understanding of the production and quality control activities of the manufacturer;
- assessment of product data and information on safety, efficacy and quality submitted by the manufacturer, including product formulation, manufacture and test data and results;
- assessment of the manufacturing site's adherence to GMP, and its consistency in production and quality control of starting materials, with specific emphasis on active pharmaceutical ingredients, and finished product;

¹ Other dexamethasone products with similar strengths as the ones listed may be considered. Please contact PQT.

- assessment of clinical testing units or organizations (i.e. parties performing one or more clinical trials with the product) for compliance with good clinical practices and good laboratory practices, as appropriate;
- random sampling and testing of medicines supplied.

Once WHO is satisfied that quality assessment has been completed for the manufacturer of the relevant starting materials, the finished pharmaceutical product, and the clinical testing units, and that the product meets WHO recommended standards, the product (as produced at the specified manufacturing site) is added to the [WHO List of Prequalified Medicinal Products](#).

ARTICLE 5. REFERENCES AND FURTHER INFORMATION

Dexamethasone

1. RECOVERY Trial, N Engl J Med 25 February 2021

<https://www.nejm.org/doi/full/10.1056/NEJMoa2021436>

Tocilizumab and Sarilumab

2. RECOVERY Trial, The Lancet 1 May 2021

<https://www.thelancet.com/action/showPdf?pii=S0140-6736%2821%2900676-0>

3. REMAP-CAP Study, N Engl J Med 22 April 2021

<https://www.nejm.org/doi/full/10.1056/NEJMoa2100433>