Coronavirus disease (COVID-19) pandemic
Product specific requirements for currently invited IL-6 inhibitors (tocilizumab and sarilumab)

IL-6 Inhibitors

Tocilizumab is a recombinant humanized anti-interleukin (IL)-6 receptor monoclonal antibody approved by different SRAs (Stringent Regulatory Authorities) for the treatment of certain inflammatory disorders including rheumatoid arthritis and cytokine release syndrome induced by chimeric antigen receptor T cell (CAR-T cell) therapy.

Sarilumab is a fully human IgG1 monoclonal antibody that binds specifically to both soluble and membrane-bound IL-6 receptors (sIL-6Rα and mIL-6Rα), and has been shown to inhibit IL-6-mediated signaling through these receptors. It is approved by different SRAs for treatment of moderately to severely active rheumatoid arthritis in selected patients. It is hypothesized that modulating the levels of proinflammatory IL-6 or its effects may reduce the duration and/or severity of COVID-19 illness. To date, no IL-6 inhibitor is approved by any SRA for the treatment of COVID-19.

The WHO Guideline Development Group has issued a statement on the use of tocilizumab and sarilumab that included recommendations based on results from the Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP[i]). The WHO GDG has also reviewed results of the open-label, pragmatic Randomized Evaluation of COVID-19 Therapy (RECOVERY[ii]). Based on the GDG statement of positive benefit/risk in COVID-19, the WHO Prequalification Unit has developed a prequalification procedure for tocilizumab and sarilumab, following either of two pathways:

1) abridged assessment of tocilizumab and sarilumab biotherapeutic products (BTPs), or their corresponding similar biotherapeutic products (SBPs), which have been approved by SRAs and marketed in the country of registration (hereinafter referred to as "Abridged Assessment"); or
2) full assessment of SBPs for tocilizumab and sarilumab that have been registered by non SRAs (based on a reference biotherapeutic product (RBP) approved by a SRA) (hereinafter referred to as "Full Assessment")

This document addresses technical, communication, policy and other aspects as applicable to the specific medicines invited under the current prequalification (PQ) procedure as detailed below[1].

[1] Please also refer to the applicable principles detailed in the "WHO Pilot Procedure for Prequalification of BTPs: rituximab and trastuzumab" (https://extranet.who.int/pqweb/sites/default/files/documents/01_Pilot_PQ_anticancer_procedure_feb2020.pdf)

Based on experience gained during the PQ process, WHO reserves the right to revise the prequalification procedure.

1) **abridged assessment of tocilizumab and sarilumab BTPs, or their corresponding SBPs, which have been approved by stringent regulatory authorities (SRAs) and marketed in the country of registration (hereinafter referred to as "Abridged Assessment")[2];**

- Applicants must request a pre-submission meeting (PSM) to discuss their product. If the product is deemed eligible for submission according to the published EOI process, the following documents are required:
- A covering letter, expressing interest in participating in the WHO prequalification procedure and confirming that the information submitted in the product dossier is complete and correct
- A copy of the marketing authorization, or equivalent thereof, issued by the reference SRA demonstrating that the product is registered or licensed in accordance with the reference SRA's requirements. If applicable, a copy of the latest renewal of the marketing authorization should also be provided.
- If available, a copy of the current WHO-type certificate of a pharmaceutical product issued and fully completed, including answers to each question, by the reference SRA.
- A list of the SRA-approved manufacturer(s) of the drug substance (DS) and drug product (DP), including manufacturers of intermediates, primary packaging sites and DS and DP release-testing sites for both the DS and DP, with the physical address of the manufacturing site(s) (and unit if applicable).
- A declaration that the product offered for PQ is, and will be after PQ, identical in all aspects - including but not limited to composition/formulation, manufacturing, specifications, packaging and DS manufacturer(s) - to the SRA approved product.
- Clinical data supporting the use of the product in the management of Covid-19 infection, when available.
- There is no need to submit any quality/GMP documentation.
- The WHO prequalification-specific addendum to the RMP as detailed on the PQ BTP web page (https://www.who.int/medicines/regulation/RMP_AddStructureDec2019-2.pdf?ua=1P).
- Safety specification, pharmacovigilance plan, risk management plan (RMP) and post-marketing safety reports. It is expected that all available information at the time of

[2] This section applies to product approved by an SRA for SARS-CoV2 indication or for other therapeutic indications. For further guidance please refer to the applicable principles and documentation detailed in the "WHO Guidelines on submission of documentation for abridged assessment" (https://extranet.who.int/pqweb/sites/default/files/documents/03_Pilot_PQ_anticancer_AbridgedPathway_Feb2020.pdf)

submission specifically related to the SARS-CoV2 indication is discussed/addressed in each section of the SRA-approved RMP, specifically:

- Populations not studied in clinical trials, exposure of special populations included or not in clinical development programs (considered as missing information)
- Identified and potential risks specific to SARS-CoV2 infected patients including characterization of the risk in groups with potential higher risk, e.g. immunocompromised patients, patients with comorbidities. Discussion of preventability and its potential impact on the benefit/risk
- Missing information (e.g. elderly, paediatric) specific in SARS-CoV2 infected patients and potential impact on benefit/risk
- Description of on-going/planned additional pharmacovigilance activities such as non-clinical, clinical or epidemiological studies (interventional or non-interventional), and the reason they are needed. Description of the type of study (e.g. long-term follow-up extensions of ongoing clinical trial(s), further effort to evaluate the missing data). Information on the study population should be part of the study description. Clear milestones and due dates should be provided (e.g. submission of final study report by 31/01/2022). Description (e.g. study type, study population, milestones and due date) of on-going/planned post-authorization efficacy studies (PAES) and the reason they are needed.
- Risk minimization measures, including additional measures and evaluation of the effectiveness of risk minimization activities.

2) **Full assessment of SBPs for tocilizumab or sarilumab that have been registered by non SRAs (based on a Reference biotherapeutic product (RBP) approved by an SRA) (hereinafter referred to as "Full Assessment")[3];**

- Applicants must request a pre-submission meeting (PSM) to discuss their product. If the product is deemed eligible for submission according to the PQ process, the following apply:
- A covering letter, expressing interest in participating in the WHO prequalification procedure and confirming that the information submitted in the product dossier is complete and correct
- The data for an SBP should follow the structure of the CTD format containing the required quality, GMP, non-clinical and clinical information for the applicable sections.

[3] For further guidance please refer to the applicable principles and documentation detailed in the "WHO Guidelines on submission of documentation for full assessment" (https://extranet.who.int/pqweb/sites/default/files/documents/02_Pilot_PQ_anticancer_fullPathway_20Feb2020.pdf)

In addition, such applications should fulfil the specific requirements detailed in the ICH M4 guideline.

- Head-to-head comparison of a biotherapeutic product with a SRA-licensed reference biotherapeutic product (RBP) with the goal of establishing similarity of quality, safety and efficacy.
- Safety specification, pharmacovigilance plan, risk management plan (RMP) and post-marketing safety reports. It is expected that all available information at the time of submission specifically related to SARS-CoV2 indication is discussed/addressed in the RMP and specifically:
    - Populations not studied in clinical trials, exposure of special populations included or not in clinical development programs (considered as missing information)
    - Identified and potential risks specific to SARS-CoV2 infected patients including characterization of the risk in groups with potential higher risk, e.g. immunocompromised patients, patients with comorbidities. Discussion of preventability and its potential impact on the benefit/risk
    - Missing information (e.g. elderly, paediatric) specific in SARS-CoV2 infected patients and potential impact on benefit/risk
    - Description of on-going/planned additional pharmacovigilance activities such as non-clinical, clinical or epidemiological studies (interventional or non-interventional), and the reason they are needed. Description of the type of study (e.g. long-term follow-up extensions of ongoing clinical trial(s), further effort to evaluate the missing data). information on the study population should be part of the study description. Clear milestones and due dates should be provided (e.g. submission of final study report by 31/01/2022). Description (e.g. study type, study population, milestones and due date) of on-going/planned Post-authorization Efficacy Studies (PAES) and the reason they are needed.
    - Risk minimization measures, including additional measures and evaluation of the effectiveness of risk minimization activities.

[i] REMAP-CAP Study, N Engl J Med 22 April 2021
https://www.nejm.org/doi/full/10.1056/NEJMoa2100433

[ii] RECOVERY Trial, The Lancet 1 May 2021
https://www.thelancet.com/action/showPdf?pii=S0140-6736%2821%2900676-0