

Request to Submit Stability Data with the Submission of Documentation for Prequalification of Finished Pharmaceutical Products (FPPs) Approved by Stringent Regulatory Authorities (SRAs)

Applicants applying for prequalification of finished pharmaceutical products (FPPs) via the stringent regulatory authority (SRA) route should submit, with their application, the stability data submitted for approval of the label storage condition and shelf life by the reference SRA. If available, zone IVb stability data (data generated at $30\pm 2^{\circ}\text{C}/75\pm 5\%\text{RH}$) on the primary or production batches of the product in the same packaging as approved for marketing of the FPP in the reference SRA's country/region should also be provided. The data should be provided in tabulated format, with appropriate discussion.

If zone IVb stability data are not available by the time of submission, applicants should initiate as soon as possible long-term stability testing at zone IVb storage conditions in the same packaging as approved by the reference SRA for marketing of the product. Once available, the full long term zone IVb data (at minimum 12 months data to assess possible extrapolation), together with the data submitted for approval of the label storage condition and shelf life by the reference SRA (i.e. the full data set), should be submitted to WHO). This can be done after prequalification of the product. A written commitment should be provided confirming that at least two batches of the product will be put, as soon as possible, on long-term stability testing at zone IVb storage conditions in the same packaging as approved by the reference SRA for marketing of the product and that the SRA approved shelf life specifications and test procedures will apply. An indication of the date when the 12 months data can be expected should be included.

The requested data are important in lieu of WHO's stability requirements and to advise the procurement agencies (and recipient countries) of the WHO recommended label storage conditions for the FPP, i.e. storage conditions based on the WHO prequalification convention. This is important for safe use of medicinal products in the recipient countries with zone III, IVa and IVb climatic conditions.

WHO PREQUALIFICATION REQUIREMENTS FOR STABILITY STUDIES OF FPPS

The following principle is formulated in the notice *Requirements for Stability Studies of Finished Pharmaceutical Products* (March 2016) available on the WHO prequalification website:

"Stability data must demonstrate stability of the medicinal product throughout its intended shelf- life under the climatic conditions prevalent in the target countries. Merely applying the same requirements applicable to other markets could potentially lead to substandard products, e.g. stability studies conducted for countries in Climatic Zone I/II when the products are supplied in Climatic Zones III and IV."

The notice defines the following stability testing requirement:

"When evaluating applications, WHO assumes that all the medicines prequalified will be used in all sub-zones of Climatic Zones III and IV, unless otherwise properly justified by the applicant and confirmed by WHO. Therefore, in order to safeguard product quality throughout its entire intended shelf-life, stability studies under the conditions defined for Climatic Zones IVb should be performed and the data submitted, i.e. the shelf-life should be established based on complete long-term data at $30\pm 2^{\circ}\text{C}/75\pm 5\%\text{RH}$."

This principle and requirement have been successfully implemented for products prequalified via the generic route. However, products submitted for prequalification via the SRA route often do not comply with this, mainly due to SRA storage requirements (zone II climatic condition). Typically, the stability testing has been carried out at zone II long term conditions and at accelerated conditions according to SRA requirements.

Furthermore, the storage statements in the SRA-approved product information may be inappropriate for distribution in countries with zone III, IVa/IVb climatic conditions due to the labelling convention of the SRA (zone II country). See, for instance, Table 1.

SRA GUIDE: BASIC REQUIREMENTS FOR PRODUCT INFORMATION

WHO's "Guidelines on submission of documentation for prequalification of finished pharmaceutical products approved by stringent regulatory authorities"¹ (SRA guide) include the following important statements:

- "[Provide] a statement confirming that for WHO prequalification, the FPP – including but not limited to composition/formulation, strength, manufacturing, specifications, packaging, product information – will, at the time of submission and after prequalification, in all respects be the same as the product registered with the reference SRA."
- "WHO may request additional data, when considered necessary for the use of the product in populations, settings or regions relevant for prequalified products. If necessary, this additional information, relevant for use of the product within the scope of the Prequalification Programme, will be included in the WHO public assessment report (WHOPAR) as a separate piece of information. Such information could be communicated to the reference SRA where appropriate. The SRA-approved product information will not be changed."

The English language version of the product information as approved by the reference SRA is either published in the corresponding WHOPAR on the WHO prequalification website and/or a link is provided to the product information on the reference SRA's website. In the spirit of the guideline, WHO will not change the SRA-approved product information, including the storage condition, but will add additional information such as the WHO recommended storage condition in other parts of the WHOPAR of the product if deemed necessary.

The additional information will be included as a note on the opening WHOPAR page of the product, referring to WHOPAR Part 1 where the recommended storage statement is included. Examples of recommended storage statements are provided in Table 1.

It is furthermore recommended that procurement agencies and/or NMRAs label batches to be supplied to zone III, IVa and IVb countries with the WHO recommended storage statement.

SRA STORAGE STATEMENTS AND WHO-RECOMMENDED STORAGE STATEMENTS

The reference SRAs are currently all from zone II areas (Europe, USA, Canada), and so their label storage conditions and stability data requirements are related to zone II climatic conditions. Differences are seen with respect to the storage statements associated with a given set of stability data, compared to products intended for zones III and IVa/IVb.

Typical examples of the storage statement in SRA-approved product information and the corresponding WHO recommended storage statement to appear in the product's WHOPAR are provided in Table 1.

Upon provision of zone IVb stability data submitted post-prequalification, the WHO recommendation will be changed if warranted by the results. See, for instance, the second entry in Table 1. This is particularly advantageous for both the applicant and the procurement agency.

¹ [Guidelines on submission of documentation for prequalification of finished pharmaceutical products approved by stringent regulatory authorities](#), WHO Technical Report Series 986, Annex 5, 2014.

POSTING OF STORAGE CONDITIONS IN THE WHO PREQUALIFICATION LIST

The storage statement and the established shelf-life are included for each prequalified product in the list of prequalified products on the WHO prequalification website. This will allow procurement agencies instant access to these important features of prequalified products.

Table 1: Examples of SRA-approved and WHO prequalification recommended storage statements based on available data.

Storage statement in SRA product information (labels)	Stability data available [stability outcome]	WHO prequalification recommended storage statement
This medicinal product does not require any special storage conditions (or similar, i.e. no temperature mentioned) [EU]	Zone II + accelerated [FPP is stable at long term conditions, with no significant change at accelerated]	Do not store above 25°C. Protect from moisture.
This medicinal product does not require any special storage conditions. [EU]	Zone II + Zone IVb + accelerated [FPP is stable at long-term conditions (zones II and IVb), with no significant change at accelerated]	Do not store above 30°C.
Do not store above 30°C [EU]	Zone IVa + accelerated [FPP is stable at long term conditions, with significant change at accelerated]	Do not store above 30°C. Protect from moisture. Avoid excursions above 30°C.
Store at 15°C to 30°C [US, Canada] OR Store at 25°C; excursions permitted to 15°C to 30°C [US] OR Store at controlled room temperature (15–30°C) [Canada]	Zone II + accelerated [FPP is stable at long-term conditions, with no significant change at accelerated]	Do not store above 25°C. Protect from moisture.

Note: the above are general examples. The storage statement will be determined case-by-case based on the actual stability data of the dossier in question.