Step by step instructions to assist manufacturers in the implementation of the WHO Collaborative Registration Procedure (CRP) for vaccines

Implementation of the CRP is in the hands of country NRAs and WHO, however manufacturers are the third party required to make this procedure work. Manufacturers can contribute significantly to foster expanded and efficient use of the procedure. Although it is clearly WHO's job to share reports and address possible questions from the NRAs, there's much that can be done by manufacturers. The following is a step by step guide to foster implementation of the CRP

Preparation of the registration dossier for the NRA in the country of origin
It is likely that your NRA will have a required format and specific requirements to be met. If your NRA is an ICH observer or member, it is also likely that in addition to their current national format they might accept the submission of an ICH CTD for registration, even if it is slightly different from their format. This is likely because as members they must adopt the ICH guideline documents and proposed CTD format. Hence, you should request their agreement to make the submission in ICH CTD. It is a request for a flexible approach towards submissions in CTD. Furthermore, to increase alignment among manufacturers; DCVMN proposes to prepare the ICH CTD in accordance with the EU Notice for Applicants. Links to the two documents to be used is given below

https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-2/b/update_200805/ctd_05-2008_en.pdf

https://www.ema.europa.eu/en/ich-m-4-q-common-technical-document-registration-pharmaceuticals-human-use-quality

Preparation of the prequalification dossier
The preparatory work for a vaccine submission for WHO prequalification should include the development of an ICH CTD. The guidance for preparation of such dossier is best provided in the EU Notice to applicants as explained above.

Module 1 has to follow WHO format and include all the programmatic suitability related information. This can be found at the link below

https://extranet.who.int/pqweb/medicines/collaborative-registration-faster-registration

Preparing the dossier in this format will lead to an alignment among manufacturers

Submission of registration application in an importing country where the NRA adopts the CRP

1.-- Search on the medicines list of countries using CRP for drugs and invite those NRAs to use the procedure for a vaccine which you wish to register in that country. The link to the countries' list is given below

https://extranet.who.int/prequal/content/collaborative-registration-faster-registration

2.- Only vaccines that have been recently prequalified can be considered for CRP in countries. This is because these are the vaccines for which the WHO reports comply with current reporting standards. Older reports may not meet current criteria.

3.- The submission to the importing country NRA adopting the CRP can be made with the same file as submitted to WHO, although they may have some additional country specific requirements to be met. WHO TRS 996, annex 8: 2016.

4.- The manufacturer can ask the NRA to accept the module 1 in WHO format with the addition of any other information required by the NRA. The link to the relevant TRS is given below

https://www.who.int/immunization_standards/vaccine_quality/WHO_TRS_996_annex08.pdf

5.- During the registration process, the NRA may pose questions to WHO which will be answered by the PQ unit, but can also pose questions directly to the manufacturer or ask for additional information. At any of these steps, the process can be stopped or delayed. In order to prevent any bottlenecks or unnecessary delays in the process, it is of utmost importance to follow up on weekly basis with WHO. The Regulatory and Safety unit (Reg) at WHO is responsible for this procedure, however since the reports being shared belong to the PQ unit, it might be advisable to copy all communications to the PQ unit, and to the Director of the Regulatory and Prequalification Department at WHO. Active follow up may be an effective mechanism to move the process forward.

Management of PACs in countries adopting the CRP.

Post-Approval Changes

The CRP procedure, starts with a facilitated registration in countries and continues with timely reporting of post-approval changes.

The following provides guidance for the submission of variations:

- Variations are to be submitted to the NRA of the CRP adopting country not later than 30 days after acceptance by the PQT to ensure sameness of the products throughout the product lifecycle.
- Variations submissions to NRAs should indicate that the product has been registered by the CRP registration pathway, with the same dossier, including any additional information based on PQT and evidence of such approval by the PQ team.
- The NRA may consider performing verification based on the shared assessments of the variation by the PQT, instead of independent review, and issue an acknowledgment of receipt or approval within 30 days.

- All information exchanges are managed through the restricted-access website provided by WHO for the purpose.
- Within 30 days of obtaining access to the information and documentation from WHO/PQT, each participating authority informs WHO/PQT through the restricted-access website if and to what extent a variation of a WHO-prequalified product is not followed by the same accepted variation of the nationally-registered product and, as a consequence, the nationally-registered product is no longer the same as the WHO-prequalified product. The variation approved by WHO/PQT will be considered by WHO/PQT as accepted by the NRA on a non-objection basis 30 days after information-sharing, unless and until the NRA informs WHO/PQT otherwise.

Detailed information on the communication of variations to participating NRAs is given in the Collaborative Registration Procedure document that can be found at the link below

https://www.who.int/immunization_standards/vaccine_quality/WHO_TRS_996_annex08.pdf

NOTE: The management of variations within CRP proves challenging for medicinal products. The use of CRP for vaccines being slower, has not yet rendered much information on the challenges for submission of variations. This is the next step in the process, but firstly we need to increase the use of the procedure for vaccines.

Expected Outcome

The implementation of the CRP would lead in a natural manner to the alignment in dossier format (modules 2 to 5) between manufacturers both for WHO-PQ and importing countries registration submissions. It could potentially also lead to alignment in module 1 if countries adopting the CRP agree to accept the WHO module 1 format. Furthermore, if the NRA in the country of origin flexibly accepts the same dossier format, only one dossier would need to be prepared for the three levels of authority, with the exception of the specific requirements from each of these levels.

Expanded use of CRP with improved efficiency (meeting the 90 days timeframe) would lead to increased interest in WHO PQ for vaccines and increased reliance in this process.