Comments and suggestions from reviewer

Title: COLLABORATIVE PROCEDURE BETWEEN THE WORLD HEALTH ORGANIZATION (WHO) AND NATIONAL REGULATORY AUTHORITIES IN THE ASSESSMENT AND ACCELERATED NATIONAL REGISTRATION OF WHO-PREQUALIFIED IN VITRO DIAGNOSTICS (IVDS)

(WHO/CRP/DRAFT/2020)

Reviewer (name, position, full contact details):

Jamie Wolszon
Associate Vice President, Technology & Regulatory Affairs
AdvaMedDx
701 Pennsylvania Avenue, Northwest, Suite 800, 20004
202-434-7230

Sections/page and line No.	Original Text	Comment	Suggested Amendment	Internal Use Only [blank]
General/Overall comment				
On behalf of AdvaMedDx, a Division of the Advanced Medical Technology Association (AdvaMed), we respectfully submit comments to this public consultation. AdvaMedDx member companies produce advanced, *in vitro* diagnostic tests that facilitate evidence-based medicine, improve quality of patient care, enable early detection of disease and reduce overall health care costs. Functioning as an association within AdvaMed, AdvaMedDx is the only multi-faceted policy organization that deals exclusively with issues facing IVD companies in the United States and abroad.				
AdvaMedDx supports WHO's effort to embrace principles of reliance with this proposed collaborative procedure (CP) pursuant to which National Regulatory Authorities (NRAs) would rely upon WHO's prequalification assessment of an *in vitro diagnostic* (IVD) rather than insist upon a separate marketing authorization. We also note other WHO efforts to promote reliance and appreciate WHO's language in this and other documents indicating that reliance promotes efficient use of limited resources and timely access to safe and efficacious IVDs. However, we have identified certain provisions within the document that we believe would undermine this goal and compromise the proposed CP if not revised.				
The document envisions that NRAs would rely upon a WHO prequalification assessment but does not similarly contemplate that WHO would rely upon NRAs. To realize the WHO stated goals of this program, we believe this reliance must be reciprocal. As we have in the past, AdvaMedDx recommends WHO rely upon decisions of the NRAs,				

Sections/page and line No.	Original Text	Comment	Suggested Amendment	Internal Use Only [blank]
including considering recognizing regulatory authorizations, clinical and bench testing, eliminating the need to repeat Performance Evaluations, and inspections. In our member companies' experience, WHO prequalification assessments (even those that use the abbreviated process) often take significantly longer than marketing authorization from jurisdictions such as the United States, European Union, Australia or Japan. We have been informed that one of the primary reasons for more lengthy review times is that the WHO prequalification process may require the Performance Evaluation to be repeated despite already being performed by the manufacturer and utilized by a regulatory authority, such as those within the United States, Australia, Japan or the European Union, to authorize the IVD. Our recommendation that WHO also rely on the NRAs decisions and other internationally recognized standards such as Medical Device Single Audit Program (MDSAP) or Good Manufacturing Practice (GMP) certifications would promote the WHO's organizational objective to "improve access to essential medicines and products." Therefore, our recommendation is supported by the WHO Constitution, which directs WHO to perform duties "consistent with its objective."				
Under the proposed program, manufacturers would need to agree that confidential information is shared with WHO and NRAs, without having control over the information. For the program to be a success, there must be adequate protections of this exchange of confidential information.				
WHO should ensure adequate flexibility in the concept of "sameness" to accommodate the unique aspects of IVDs. IVDs are frequently updated to reflect innovation. These updates can be iterative and, in some cases, rapid to ensure patients have access to the safest, most innovative IVDs. Therefore, IVDs are unlikely to be identical to the product in the original submission in light of this innovation. Furthermore, due to differences in regulation, regulators may or may not require review of IVD changes. IVD improvement should not render recognition and reliance unusable. If this important point is not clarified, the WHO may risk inadvertently minimizing the usefulness of reliance and recognition across the total product life cycle. We recommend the WHO acknowledge that the IVD may be improved subsequent to prequalification assessment and such improvements/changes do not render the original prequalification assessment unusable. The WHO guidance should allow manufacturers to supplement the original submission with reasonable evidence that IVD changes did not significantly alter it from its original submission and that updates were appropriately controlled.				
Background				
Introduction				

Sections/page and line No.	Original Text	Comment	Suggested Amendment	Internal Use Only [blank]
Section 2, Introduction, page 6, line 65	Text currently not present.	To meet the goals of the CP and advance the WHO's objective to "improve access to essential medicines and health products," we recommend that WHO reciprocate reliance and recognition principles. Doing so will enhance WHO's ability to achieve the program goals and ensure patients gain access to safe and effective products in the most efficient manner that maximizes WHO's limited resources. Additionally, we recommend the remainder of the document be updated to reflect the principles of recognition and reliance are reciprocated.	Add the text below: To further accelerate access to safe and effective IVDs in a manner that wisely uses limited regulatory resources, WHO intends to reciprocate recognition and reliance on regulatory authorizations, clinical and bench testing, Performance Evaluations, and inspections.	
Section 2, page 6, lines 67-70	This Collaborative Procedure has been developed based on the above-mentioned considerations to enhance timely access to WHO-prequalified products in countries, to ensure that the product in countries is the same as the one which is WHO-prequalified and to provide a model for regulatory information exchange between countries.	The document envisions that NRAs would rely upon a WHO prequalification assessment but does not similarly contemplate that WHO would rely upon NRAs. We believe this reliance should be reciprocal. As we have in the past, AdvaMedDx recommends WHO rely upon decisions of the NRAs, including recognizing regulatory authorizations, clinical and bench testing and eliminating the need to repeat Performance Evaluations and inspections. In	We recommend making the following changes: This Collaborative Procedure has been developed based on the above-mentioned considerations to enhance timely access to WHO-prequalified products and already authorized IVDs from qualitied authorities in countries, to ensure "sameness" can be demonstrated, that the product in countries is the same as the	

Sections/page and line No.	Original Text	Comment	Suggested Amendment	Internal Use Only [blank]
		our member companies' experience, WHO prequalification assessments (even those that use the abbreviated process) often take significantly longer than marketing authorization from jurisdictions such as the United States, European Union, Australia or Japan. We have been informed that one of the primary reasons for more lengthy review times is that the WHO prequalification process may require the Performance Evaluation to be repeated despite already being performed by the manufacturer and utilized by a regulatory authority to authorize the IVD. Our recommendation that WHO also rely on the NRAs would promote the goals of efficient use of WHO resources and timely access to safe and efficacious IVDs in WHO member countries. Also, as discussed above, WHO should interpret the concept of same in a manner that embraces the frequent updates to IVDs to reflect innovation.	one which is WHO-prequalified and to provide a model for regulatory information exchange between countries. It is important to recognize that IVDs are frequently modified subsequent to the original regulatory authorization. Recognition and reliance principles still apply to a modified IVD, even if the modification did not require subsequent regulatory authorization. Manufacturers should be permitted to supplement the original submission with reasonable evidence to demonstrate that IVD modifications did not significantly alter the IVD from its original submission, and that updates were appropriately controlled according to an established quality system.	

Sections/page and line No.	Original Text	Comment	Suggested Amendment	Internal Use Only [blank]
Aim and objectives of the Collaborative Procedure				
Section 2.1, page 6, lines 73-78	This Collaborative Procedure aims to provide a convenient tool for NRAs wishing to enhance their premarketing evaluation and registration system by taking advantage of the WHO prequalification assessment, in-line with the Procedure for WHO Prequalification of In Vitro Diagnostics (3) and the Essential Principles of Safety and Performance of Medical Devices and IVD Medical Devices	The document envisions that NRAs would rely upon a WHO prequalification assessment but does not similarly contemplate that WHO would rely upon NRAs. We believe this reliance should be reciprocal. As we have in the past, AdvaMedDx recommends WHO rely upon decisions of the NRAs, including considering recognizing regulatory authorizations, clinical and bench testing and eliminating the need to repeat Performance Evaluations and inspections. In our member companies' experience, WHO prequalification assessments (even those that use the abbreviated process) often take significantly longer than marketing authorization from jurisdictions such as the United States, European Union, Australia or Japan. We have been informed that one of the primary reasons for more lengthy review times is that the WHO prequalification process may require the Performance	WHO should rely upon decisions of the NRAs, to include recognizing regulatory authorizations, clinical and bench testing, eliminating the need to repeat Performance Evaluations and inspections.	

Sections/page and line No.	Original Text	Comment	Suggested Amendment	Internal Use Only [blank]
		Evaluation to be repeated despite already being performed by the manufacturer and utilized by a regulatory authority to authorize the IVD. Our recommendation that WHO also rely on the NRAs would promote the goals of efficient use of WHO resources and timely access to safe and efficacious IVDs in WHO member countries.		
Section 2.1, page 6, lines 80-87	Describe the procedure for accelerating national registrations of WHO-prequalified IVDs in participating NRAs based on exchange of assessment, manufacturing site inspection and performance evaluation outcomes between the WHO Prequalification Team (WHO-PQT) and the NRAs. Provide a resource for manufacturers or applicants with prequalified IVDs, and participating NRAs to implement and facilitate national registrations for prequalified IVDs.	The document envisions that NRAs would rely upon a WHO prequalification assessment but does not similarly contemplate that WHO would rely upon NRAs. We believe this reliance should be reciprocal. As we have in the past, AdvaMedDx would encourage WHO to rely upon decisions of the NRAs, including considering recognizing regulatory authorizations, clinical and bench testing and eliminating the need to repeat Performance Evaluations. In our member companies' experience, WHO prequalification assessments (even those that use the abbreviated process) often take significantly longer than marketing authorization from jurisdictions such as the United	WHO should rely upon decisions of the NRAs, including considering recognizing regulatory authorizations, clinical and bench testing, eliminating the need to repeat Performance Evaluations, and inspections.	

Sections/page and line No.	Original Text	Comment	Suggested Amendment	Internal Use Only [blank]
		States, European Union, Australia or Japan. We have been informed that one of the primary reasons for more lengthy review times is that the WHO prequalification process may require the Performance Evaluation to be repeated despite already being performed by the manufacturer and utilized by a regulatory authority to authorize the IVD. Our recommendation that WHO also rely on the NRAs would promote the goals of efficient use of WHO resources and timely access to safe and efficacious IVDs in WHO member countries.		
Glossary				
Principles and general considerations				
Section 3.2, page 10, lines 180-189	WHO-PQT and participating NRAs receive applications for the same IVD product. Within the context of this Collaborative Procedure, the	We recommend WHO remove certain requirements for sameness that could render the principles of recognition and reliance unusable. In addition,	WHO-PQT and participating NRAs receive applications for the same IVD product. Within the context of this Collaborative Procedure, the	

Sections/page and line No.	Original Text	Comment	Suggested Amendment	Internal Use Only [blank]
	same product is characterized by: • the same product name, • the same specifications, including the same regulatory version and the same product code, • the same site of manufacture and quality management system, • the same data on quality, safety and performance, • the same design, with the same components from the same suppliers, • the same information, labelling and packaging including instructions for use and intended use.	for the reasons listed above, we recommend WHO add a statement that allows manufacturers to supplement the original submission with reasonable evidence that IVD changes did not significantly alter the IVD from its original submission and that updates were appropriately controlled. Remove the same regulatory version and the same product code: We recommend that WHO remove the cited language requiring the same regulatory version and product codes to be the same. As stated above, IVDs change frequently. Product codes may need to vary due to country-specific requirements (e.g., national labeling). This subtlety needs to be accommodated. This is one specific example of our general comment that WHO should be sufficiently flexible in interpreting the concept of "*same"*. Remove Same Manufacturing Site and allow for an equivalent Quality System: We recommend the WHO remove the cited example that the IVD be produced at the same	same product is characterized by: • the same or similar product name, • the same specifications, • the same or equivalent quality management system, • the same or similar data on quality, safety and performance, • the same design, with the same components, • the same or similar information, labelling and packaging including instructions for use and intended use. To ensure the term "same" is not taken literally, and to account for the changes made to IVDs to improve and innovate, we also recommend adding the statement below: It is important to highlight that IVDs may frequently be modified subsequent to the original regulatory authorization. Recognition and reliance principles still apply to a modified IVD, even if the modification did not require subsequent regulatory authorization. Manufacturers	

Sections/page and line No.	Original Text	Comment	Suggested Amendment	Internal Use Only [blank]
		manufacturing site to leverage the CP. We believe it should not be a requirement that the IVD be produced at the same manufacturing plant in order to leverage reliance principles and the CP. The IVD community has longstanding controls to qualify and confirm adherence to good manufacturing practices (GMPs) and internationally recognized standards such as ISO 13485. Through these certifications, the quality and control of production practices is standardized and verified to ensure the IVD is consistently produced at the same quality standard. Therefore, requiring the IVD to be produced at the same plant does not enhance the safety or effectiveness of the IVD, yet increases the complexity and burden of production requirements. This a specific example of our general comment that WHO should be sufficiently flexible in its approach to sameness. Remove the Same Suppliers Requirement: We recommend removing the requirement to demonstrate the same supplier(s). It is highly unlikely	should be permitted to supplement the original submission with reasonable evidence to demonstrate that product modifications did not significantly alter the product from its original submission, and that updates were appropriately controlled according to an established quality system.	

Sections/page and line No.	Original Text	Comment	Suggested Amendment	Internal Use Only [blank]
		that suppliers have remained the same since the original submission. Manufacturers must adhere to robust regulatory requirements to qualify and control suppliers. These requirements ensure the performance of the product is not adversely affected while allowing manufacturers to maintain flexibility in suppliers. Therefore, requiring that the original submission have the same suppliers is not feasible and would undermine the principles of recognition and reliance. Product Information, labelling, and IFU: We recommend adding “or similar” to the requirements for packaging, labelling and IFUs (instructions for use). Information regarding IVDs may be updated frequently, and many countries have in-country requirements for packaging, labelling, and instructions for use that differ from other countries. Until such requirements are harmonized globally, manufacturers should be permitted to demonstrate the same or similar.		

Sections/page and line No.	Original Text	Comment	Suggested Amendment	Internal Use Only [blank]
Section 3.4, page 12, lines 224-252	WHO-PQT, with the agreement of the applicant/manufacturer of the WHO-prequalified product, shares the full outcome of prequalification assessments, manufacturing site inspections and performance evaluations, including final assessment and inspection reports with participating authorities, under appropriate obligations of confidentiality and restrictions of use (see below).	While the NRAs have the right to determine the level of information needed for their regulatory authorization processes, many NRAs do not require this level of information to be provided. The review of this information would increase the workload for these NRAs.	N/A	
Section 3.6, page 14, footnote 7	The regulatory time does not include the time granted to the applicant to complete missing parts of the documentation, provide additional data, or respond to queries raised by the NRA.	The document explains that "regulatory time" excludes time taken by applicant to respond to queries. However, what would constitute a reasonable query. We would appreciate clarification of what constitutes a reasonable query.	Please clarify what would constitute a reasonable query. For example, a reasonable query could be defined as a request for the minimum amount of information necessary to adequately address a relevant regulatory question or issue.	
3.6, page 14, lines 289-91	If the applicant takes a long time to complete missing parts of the documentation without any justification, to provide additional data, or to respond to other queries raised by NRAs…the participating NRA is entitled to terminate the Collaborative Procedure….	The language states that the NRA may terminate the CP if an applicant takes a "long time" to complete missing parts of relevant documentation. We believe this is too broad and subjective.	If the applicant fails to reply to the CP within a reasonable timeframe (e.g., 90 days) outlining a plan to obtain and provide the requested information, takes a long time to complete missing parts of the documentation without any justification, to provide additional data, or to respond to other queries raised by NRAs…the participating NRA	

Sections/page and line No.	Original Text	Comment	Suggested Amendment	Internal Use Only [blank]
			is entitled to terminate the Collaborative Procedure….	
3.6.2		The commitment is provided by the NRA to the WHO. The same point should also be explicit in the commitment to (contractual obligation to) applicants.		
3.6	N/A	Section 3.6 lacks a commitment from the NRA in terms of actual requirements for registration. Specifically, in numerous preceding sections (e.g., see 3.4.3), the document states that while NRAs "accept the product documentation and reports in the format in which they are routinely prepared by WHO," NRAs may still "require applicants to comply with specific requirements for local regulatory review". It is critical that any variation from the WHO-norm by any given NRA be defined and agreed in advance of an application. This must be reflected in the CP guidance and agreement documents in order for the CP to be successful.	We would propose adding a commitment from the NRA that any variation from the WHO-norm be outlined in advance of the application.	
3.8.3	Participating authorities retain the right to assess submitted data and conduct site	Consideration should be given to more narrowly defining the terms of participation for NRAs.	Please remove the cited language. While participating authorities certainly do retain	

Sections/page and line No.	Original Text	Comment	Suggested Amendment	Internal Use Only [blank]
	inspections and performance evaluations to the extent they deem appropriate.	At present, this section essentially allows NRAs to exempt themselves from actually using prequalification as a tool for registration despite having agreed to the terms and conditions of the CP. Including this language weakens the entire premise and base value of the CP exercise. National sovereignty on regulatory decisions is paramount, but as the CP is an entirely voluntary partnership entered into by the NRA, the WHO and the applicant, we see no need to include such an exemption within the terms and conditions.	these rights, we believe that including the statement here weakens the CP.	
Steps in the collaboration for national registration of a prequalified *in vitro* diagnostic				
4.7	Within 30 calendar days of receipt of the manufacturer's consent, WHO-PQT shares with the participating authority the most recent product-related information and assessment, manufacturing site inspection and performance evaluation outcomes through the restricted-access website.	The document instructs that WHO will share product data with the participating authority within 30 days of applicant consent. We believe this timeframe is too long and would recommend a shorter timeframe.	We would recommend a timeframe to share product data with the NRA that is shorter than 30 days.	
4.8		As discussed above in regard to section 3.8.3, this provision appears to suggest that NRAs, which have actively and	We would propose removing the cited language.	

Sections/page and line No.	Original Text	Comment	Suggested Amendment	Internal Use Only [blank]
		deliberately decided to participate in the CP, not actually use the benefits of the CP by including statements that NRAs may repeat the work of WHO PQT. We believe this language undermines the intent of the CP.		
4.9		We would appreciate clarification of this section. This section states that the participating authority will issue a regulatory decision within 90 calendar days, but subsequently states that the decision will be reported within 30 days. It is unclear whether this means that the total timeframe will be 120 days. We would also request that the document provide definitions for the specific actions upon the 90-day time frame need to be defined, e.g., official report/license/authorisation to the applicant of legal permission to market and associated public statement(s)/updated public record as required within that jurisdiction.	We recommend adding language to clarify the regulatory decision issued in 90 days allows the product to be marketed and that the decision to be reported within 30 days is intended to provide broader visibility of the product's availability.	

Sections/page and line No.	Original Text	Comment	Suggested Amendment	Internal Use Only [blank]
Collaboration mechanisms for post-prequalification and/or post-registration variations/changes				
Withdrawals, suspensions or de-listings of prequalified IVDs and national de-registrations				
References				
Appendix 1: National regulatory authority participation agreement and undertaking for national regulatory authority focal point (s)				
Section 3/page 33-35	N/A	The way the process is described, WHO will share decisions and information received about the product with participating countries via a secure portal. Prior to obtaining this information, each participating country is expected to sign a confidentiality agreement. AdvaMedDx would appreciate clarity from WHO as to how WHO intends to enforce	None	

Sections/page and line No.	Original Text	Comment	Suggested Amendment	Internal Use Only [blank]
		the terms of confidentiality and whether information will be compromised in any way.		
Appendix 2: Consent of WHO prequalification holder for WHO to share information with the national regulatory authority confidentially under the Procedure				
Appendix 3: Expression of interest to national regulatory authority (NRA) in the assessment and accelerated national registration, acceptance by NRA and notification of Procedure outcomes				
Appendix 4: Report on post-registration actions in respect of a product registered under the Procedure				
Other Sections				

Sections/page and line No.	Original Text	Comment	Suggested Amendment	Internal Use Only [blank]