CODEX ALIMENTARIUS COMMISSION

Food and Agriculture Organization of the United Nations

World Health Organization

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Agenda item 7

CX/PR 25/56/8-Add.1
September 2025
ORIGINAL LANGUAGE ONLY

JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX COMMITTEE ON PESTICIDE RESIDUES

Fifty-sixth Session

Santiago, Chile

8 - 13 September 2025

GUIDELINES FOR MONITORING THE STABILITY AND PURITY OF REFERENCE MATERIALS AND RELATED STOCK SOLUTIONS OF PESTICIDES DURING PROLONGED STORAGE (AT STEP 7)

Comments at Step 6 in reply to CL 2025/38-PR

submitted by

Argentina, Brazil, Chile, Colombia, Cuba, Egypt, European Union, Ghana, Indonesia, Japan, Mexico, Peru, Singapore, Thailand, United Arab Emirates, United States of America, Uruguay, AgroCare Latinoamérica

Background

1. This document compiles comments received through the Codex Online Commenting System (OCS) in response to CL 2025/38-PR[1] issued in July 2025. Under the OCS, comments are compiled in the following order: general comments are listed first, followed by comments on specific sections.

Explanatory notes on the Annex

2. The comments submitted through the OCS are hereby annexed and presented in tabulated format.

[1] https://www.fao.org/fao-who-codexalimentarius/resources/circular-letters/en/
https://www.fao.org/fao-who-codexalimentarius/committees/committee/related-circular-letters/en/?committee=CCPR

ANNEX

GENERAL COMMENTS

COMMENT	MEMBER/OBSERVER
Brazil acknowledges and appreciates the extensive efforts undertaken by the Electronic Working Group (EWG) and the Chairs in developing the current draft of the Guidelines. We are pleased to see that the majority of our previous comments were incorporated, particularly the inclusion of mixed reference materials and the flexibility with respect to analytical methods.	**Brazil**
La delegación de Chile agradece el trabajo realizado por el grupo de trabajo por medios electrónicos, y considerando que es relevante que el Codex avance en la elaboración de Directrices para realizar un seguimiento de la pureza y la estabilidad del material de referencia y soluciones madre de plaguicidas conexas durante el almacenamiento prolongado, se apoya el avance y finalización en la próxima reunión del CCPR. No obstante lo antes señalado, se deja para consideración algunos comentarios específicos: - Apéndice I del documento CX/PR 25/56/8. Se evidencia que el documento cumple con el objetivo de entregar directrices para realizar un seguimiento de la estabilidad de materiales de referencia, soluciones madres conexas y mezclas de plaguicidas como también evaluar la pureza de materiales de referencia de plaguicidas durante el almacenamiento prolongado.	**Chile**
Cuba agradece la oportunidad de hacer su comentario sobre el documento CX/PR 25/56/8, que da respuesta a la CL 2025/38-PR y en principio apoyamos que este documento avance al trámite 8 para su adopción en la 48 CAC.	**Cuba**
Egypt appreciates the valuable efforts reflected in document CL 2025/38-PR and recognizes the importance of establishing sound guidance for monitoring the stability and suitability of pesticide reference materials (RMs) and stock solutions during extended storage. Egypt specifically suggests that the following technical points need to be considered for further clarification: 1. Robust traceability mechanisms for RMs and stock solutions throughout their storage life, including documentation of conditions, handling history, and any interim analytical checks. 2. Incorporation of measurement uncertainty associated with the continued or extended use of RMs beyond their expiry, in context of method validation. 3. Clear and scientifically justified criteria for the timing and methodology of revalidation, particularly when certified values approach their defined tolerance limits. 4. Harmonization with ISO/IEC 17025 requirements, especially regarding how accredited laboratories may justify extended use of RMs within a controlled quality framework, based on objective data. 5. While ISO/IEC 17025 provides general requirements on the use of fit-for-purpose RMs, it does not explicitly address long-term use or revalidation procedures. The draft Codex guideline helps bridge this gap with more practical recommendations, but Egypt believes further refinement is essential to ensure effective global implementation and scientific consistency. 6. Alignment with the requirements of ISO 33405:2024 for Reference materials –"Approaches for characterization and assessment of homogeneity and stability" Egypt supports continued dialogue on this important topic and remains committed to contributing to the advancement of this guidance.	**Egypt**

COMMENT	MEMBER/OBSERVER
The European Union (EU) would like to thank the Electronic Working Group (eWG) chaired by India and co-chaired by Argentina and Singapore for preparation of the Guidelines for monitoring the purity and stability of reference materials and related stock solutions of pesticides during prolonged storage (CX/PR 25/56/8). The EU notes that its comments provided to the eWG have been taken on board and can support the Guidelines.	**European Union**
Japan greatly appreciates the preparation of this draft guideline by the EWG, chaired by India and co-chaired by Canada, the Islamic Republic of Iran, and Singapore. The draft guideline is almost complete. However, Japan would like to provide the following comments and, provided that these comments are taken into consideration, express its support for adoption by the CAC at Step 8. The DG SANTE document includes the following statement: "For screening purposes only, the reference standards and derived solutions may be used after the expiry date, provided that the RL can be achieved. If the pesticide has been detected, a new or certified reference standard and calibration standard solution made thereof has to be used for quantification." Recognizing this statement, as well as the phrase "they may be considered suitable for use beyond their expiry provided..." as seen in this guideline, Japan proposes using "may" instead of "can" throughout this document when referring to the use of (expired) RMs and stock solutions that meet the criteria, in order to ensure consistency with the DG SANTE document and within this document itself. For example, in paragraph 6, line 54, "can" should be replaced with "may".	**Japan**
Perú agradece por el esfuerzo emprendido. No se cuenta con observaciones, por lo que se sugiere continuar con el trámite correspondiente.	**Peru**
Singapore, as the co-chair of the electronic working group, commends the Chair, other Co-chairs and Participating Countries on their excellent work for further revising the draft document. CCPR55 had agreed to expand the scope of the guidelines to cover mixtures of pesticides. In this regard, Singapore would like to suggest that this framework document also cover monitoring the stability and purity of the standard mixtures prepared by pesticide residues laboratories by using the individual RMs purchased from RMPs, provided that the pesticide residues laboratories preparing such standard mixtures have ISO/IEC 17025 accreditation. This is because, realistically, many pesticide residues laboratories very often prepare their own standard mixtures using RMs purchased from RMPs to support their multi-pesticide residues testing work based on their specific needs for analytical scope, rather than purchasing commercial standard mixtures of RMs directly from RMPs, which are based on fixed lists of pesticides. The reliability or metrological traceability of the standard mixtures of RMs prepared by pesticide residues laboratories with ISO/IEC 17025 accreditation should be assured so long as the quality control measures as stated in para 12-19 of the draft guidance document are in place. Singapore has therefore modified para 11 of the draft guidance document to reflect its broadened applicability to cover standard mixtures prepared by pesticide residues laboratories with ISO/IEC 17025 accreditation. Singapore proposes a number of editorial and technical amendments to this document in tracked changes. Singapore supports the advancement of this Codex guidance document to Step 8 after addressing the points raised.	**Singapore**

COMMENT	MEMBER/OBSERVER
Thailand noted that superscripts used throughout this guideline are unclear as some superscripts refer to reference documents specified in Appendix II of CX/PR 25/56/8 which are just information, while the others are footnotes of which explanation are identified in the below paper.	**Thailand**
The United Arab Emirates (UAE) would like to thank the Electronic Working Group (EWG) on developing the Guidelines for monitoring the purity and stability of reference materials and related stock solutions of pesticides during prolonged storage. Please find below our general comments. UAE believes that the proposed guidelines are well aligned with our objectives concerning the extension of the shelf-life of pesticide reference materials and help to provide a practical framework for analyzing the stability and purity of reference materials beyond their expiry dates. These guidelines offer practical solutions to address challenges such as limited shelf life and the high recurring cost of pesticide standards. Laboratories in UAE already implement the described approaches as follows: • Following the Approach 1: Comparing the stability of old (expired) and new (unexpired) pesticide reference standards as described in the guidelines over the past several years as part of our internal quality procedures. Specifically, laboratories do compare the peak areas of expired and fresh neat reference materials to monitor the percentage deviation. • Adhering to the general procurement and usage criteria for pesticide reference materials as outlined in the “General Criteria” part of the guidelines. • Verifying the purity of reference materials when stored under the conditions specified by the material provider. According to the new guidelines, lowering the storage temperature may potentially extend the shelf-life. We recognize this as an area that warrants further investigation and will be evaluating its feasibility within our laboratory setup. • Including the Approach 3 for monitoring mixtures strengthens the comprehensiveness of the document and serves the needs of laboratories that utilize multi-component standard solutions. stock solutions of pesticides during prolonged storage) Conclusion: UAE recommends the adoption of these guidelines at Step 8 during the upcoming session of the Codex Alimentarius Commission (CAC48), given their positive impact on improving monitoring efficiency and promoting sustainability in pesticide residue analysis programs.	**United Arab Emirates**
The United States has concerns that there may be unintended interactions between standards provided as an RM mixture over long term storage. We have not been able to identify any published studies of such mixtures other than one (JAOAC, 2023, Wiest et al.) that mentions monitoring over 31 days storage. Without supporting studies, the United States is unsure if guidelines on mixtures is appropriate. If CCPR decides that guidelines on mixtures is appropriate, the United States suggests adding a statement to alert the user that behavior of pesticides in mixtures over long term storage has not been extensively studied and that caution should be taken when proposing to extend the life of an expired RM mixture. The United States does not support the proposal of a default extension of expiry date, as published data (including the reference by Sharma, et al.), has indicated that not all pesticides have equivalent stability in storage.	**USA**
Uruguay thanks India as Chair of the EWG, and Canada, Iran, and Singapore as Co-Chairs, for the work carried out within the electronic group and for the preparation of the working document. We consider this latest version of the document much clearer and reflects the great effort of the EWG.	**Uruguay**

COMMENT	MEMBER/OBSERVER
Enfoque 1 Esta estrategia es la más directa, confiable y ampliamente aceptada. Requiere contar con un MR nuevo para realizar la comparación, lo que limita su aplicabilidad cuando se busca evitar la compra de nuevos estándares. Sin embargo, si se dispone del nuevo lote, permite validar el anterior con un alto grado de certeza. **Enfoque 2** Sugerimos especificar las características de un PI para este uso 1. Alta estabilidad en condiciones normales y de almacenamiento prolongado: o Idealmente, no sensible a la luz, ni al oxígeno, ni a la humedad. o No volátil ni susceptible a hidrólisis u oxidación. 2. No higroscópico: o Evita variaciones de masa y concentración por absorción de humedad ambiental durante la preparación de soluciones. 3. Químicamente diferente del analito, pero: o Con respuesta similar en el detector (ej. UV, FID, MS). o Que no interfiera cromatográficamente 4. Accesible y económico: o Que esté disponible en grado analítico o p.a. (pureza ≥99%). o Que pueda comprarse en cantidades grandes, para evitar cambios de lote. No presente en las matrices reales, para que no interfiera en análisis de muestra. **Enfoque 3** Su correcta implementación es compleja y exige alta competencia técnica, ya que implica evaluar simultáneamente varios analitos en presencia de posibles degradantes y componentes de matriz. Esto requiere una separación cromatográfica robusta y métodos con capacidad de resolución suficiente para minimizar el riesgo de coeluciones. Aunque esta estrategia puede optimizar tiempo y recursos en laboratorios con experiencia en métodos multiresiduo, no es recomendable en entornos con instrumentación o validaciones limitadas.	**AgroCare Latinoamérica**

COMMENT	MEMBER/OBSERVER

CONSIDERACIONES ADICIONALES PARA TODOS LOS ENFOQUES

	Descripción	Ventajas	Inconvenientes
Verificación de pureza de pico (UV o MS)	Se comprueba que el pico del analito no esté contaminado con degradantes coeluidos.	- Aumenta la confiabilidad del análisis. - Detecta degradación invisible a nivel de área de pico.	- Requiere DAD o MS en modo adecuado. - Puede no detectar degradantes con espectros o m/z similares.
Alícuotas congeladas y selladas al vacío	Fraccionamiento del MR al recibirlo y conservación bajo condiciones controladas.	- Reduce exposición a humedad, luz y temperatura. - Menor variabilidad entre usos.	- Riesgo si no se realiza correctamente el sellado
Modelado de tendencia de estabilidad	Registro gráfico de la desviación de pureza en el tiempo.	- Permite prever la caducidad real. - Facilita decisiones objetivas sobre descarte.	- Puede ser afectado por cambios instrumentales si no se normaliza.
Clasificación de riesgo del MR	Asignación de riesgo bajo, medio o alto según la susceptibilidad del MR.	- Optimiza el uso de recursos analíticos. - Justifica distinta frecuencia de control.	- Requiere criterio técnico y conocimiento previo del compuesto.
Viales prellenados y sellados para soluciones madre	Preparación de soluciones en condiciones óptimas, selladas y almacenadas sin manipulación frecuente.	- Mayor estabilidad. - Menor riesgo de contaminación o evaporación.	- Necesita equipamiento y protocolo de preparación

SPECIFIC COMMENTS

COMMENT	MEMBER / OBSERVER
Preface (paragraphs 1-5)	
1. Pesticide residues in agricultural and food commodities have become a worldwide ~~agricultural trade concern~~agri-food concern, which has led to enforcement of strict pesticide regulations. More than 1200 pesticides are available globally to control the pests on different agricultural crops and food commodities. Analyses of pesticides at trace levels in the food chain require the use of specific Reference Materials (RMs) of known chemical purity manufactured by the Reference Material Producers (RMPs) to ensure the reliability of the test results. Accurate determination of pesticide residues in agricultural and food commodities is important for food safety control and fixation of Maximum Residue Limits (MRLs) of pesticides, thereby overcoming the related trade barriers. RMs with specified purity are also required for accurate qualitative and quantitative analysis of pesticide active ingredient(s) in technical products, formulations, and stock solutions.	**Singapore**
3. Moreover, due to supply chain constraints, some laboratories may receive RMs close to their expiry date, as mentioned in the reference material document. In such situations, the laboratories are forced to buy new standards and prepare new stock solutions more frequently than necessary. This leads to enormous amount of work and increased laboratory costs~~, especially for compounds for which stability is well understood~~. Additionally, shipping RMs by the suppliers to laboratories increases the acquisition time for procurement (a few weeks to months), creating hurdles in ~~sustainable~~ sustaining pesticide residue control programs. Consider removing this clause as the main message remains clear without it.	**Singapore**
4. There are many RMs that remain stable even after the expiry dates stated in the reference material document with no significant change in purity. Some studies[1-3] have also reported that if RMs are stored at better storage conditions than recommended by the manufacturer, provided that these conditions do not contradict those indicated by the RMP in the reference material document, the RMs are stable for much longer than the expiry dates indicated by the RMPs. Such RMs may technically be allowed to be used beyond their expiry dates if laboratory checks are in place to demonstrate that they are stable and continue meeting the purity requirements. However, the absence of guidance procedures for monitoring the stability and purity of RMs prevents their use beyond the expiry ~~dates~~dates under the ISO/IEC 17025 laboratory quality system. Suggest adding the additional text to indicate this is linked to ISO/IEC 17025 lab quality system.	**Singapore**
5. We consider it highly relevant to discuss the inclusion in the document of the "practical approach" suggested by the European Union, in which the validity of standards can be extended with default factors, provided they are stored under lower temperature conditions than those recommended by the RMP. This approach would be very beneficial for analytical laboratories, especially those in developing countries, as they would be able to extend the validity of RMs and CRMs only with adequate storage equipment. For this reason, we would like to request more information in order to discuss this matter. We therefore suggest submitting a request to the European Union for this information.	**Uruguay**

COMMENT	MEMBER / OBSERVER
Scope and objective (paragraphs 6-9)	
6. The purpose of this document is to furnish a framework that would assist the laboratories in monitoring the stability and purity of reference materials (RMs) of pesticides during prolonged storage and identifying expired RMs as indicated by the COAs of RMPs but with ~~continued~~ demonstrated continuing stability and purity through robust analytical protocols so that such materials that retain their purity as per the reference material document even after expiry can continue to be used as valid RMs. Another aspect of the proposed ~~work~~ framework is to monitor the stability of the stock solutions used for pesticide residue analysis so that those solutions that ~~continue~~ are proven to be valid can be used ~~for the~~ for accurate and reliable determination of pesticide residue levels. Suggest adding the text to strengthen the rationale for extending the expiry date of RMS. Is 'proposed framework', not 'proposed work' as this document is to serve as a Codex guidance document.	**Singapore**
8. These guidelines will enable the pesticide residue laboratories and pesticide quality control laboratories to overcome the constraints associated with short expiry periods of RMs as shown in the COAs of RMPs and use them beyond their expiry dates ~~mentioned in the reference material document~~as indicated by RMPs. After the expiration ~~date~~dates of RMPs, the RMs retaining the purity specified in the reference material document can be used as RMs or as quality control materials (QCM) for the analysis of pesticides, provided that these RMs are stored under desirable conditions ~~specified in the guidelines~~ (low temperature and ~~according to the manufacturer's instructions~~dark conditions). RMs that do not remain stable and do not show acceptable purity during prolonged storage shall not be used by laboratories for pesticide residue testing/quantitative purposes, as accurate results may not be obtained. To add pesticide quality control laboratory as later part of this paragraph talks about quality control materials (QCM). Suggest replacing with new text 'desirable conditions (low temperature and dark conditions)' to echo with para 21. Stating 'provided RMs are stored under conditions specified in the guidelines and according to manufacturer's instructions does not help extend the expiry dates as manufacturers' expiry dates for RM are set for storage under ambient temperature and they typically only guarantee the expiry dates of UNOPEN bottles of RMs. The true fact is, when pesticide residues laboratories keep the RMs under deep freezing temperature (-18 degree C or lower), the expiry dates can be much longer (up to ten years). This is what is stated in DG SANTE document 11312 (F1).	**Singapore**
9. Numeral:Párrafo 9, punto 5, tabla. Comentario de Chile:Considerando que se menciona este enfoque práctico. ¿Será parte del protocolo? Es decir, ¿Se podrá considerar la extensión de uso del MR si se almacena a menor temperatura que la estipulada por el PMR?	**Chile**
9. Ghana supports the additions made to the specified paragraphs to address the issues outlined in the document. Furthermore, Ghana supports the advancement of the proposed guidelines to Step 8 for final adoption by the 48th Session of the Codex Alimentarius Commission in November 2025.	**Ghana**

COMMENT	MEMBER / OBSERVER
General criteria (paragraphs 10-19)	
10. Los MR resultan muy costosos y en muchos casos de dificultoso acceso dadas las distancias entre los proveedores y los usuarios de estos. El objetivo del documento es "proporcionar un marco que pueda ayudar a los laboratorios a realizar un seguimiento de la estabilidad y la pureza del material de referencia (MR) de los plaguicidas durante el almacenamiento prolongado…", claramente para tratar de extender el potencial uso de los MR y así minimizar gastos innecesarios. Entendemos que no todos los laboratorios pueden tener acreditada la norma ISO/IEC 17025, más aún por cada analito. Un ejemplo son los laboratorios de muchas Autoridades Nacionales Regulatorias. Esto encarecería el proceso, que justamente pretende evitar costos extra. Sugerimos se solicite que los laboratorios sigan los lineamentos de la norma ISO/IEC 17015, sin necesidad de estar acreditados La opción de formar un cluster de laboratorios, con eje en uno que posea dicha acreditación, entendemos no es válida dado que implica el traslado de los analitos en las condiciones de temperatura indicadas.	**Argentina**
10. Los MR resultan muy costosos y en muchos casos de dificultoso acceso dadas las distancias entre los proveedores y los usuarios de estos. El objetivo del documento es "proporcionar un marco que pueda ayudar a los laboratorios a realizar un seguimiento de la estabilidad y la pureza del material de referencia (MR) de los plaguicidas durante el almacenamiento prolongado…", claramente para tratar de extender el potencial uso de los MR y así minimizar gastos innecesarios. Entendemos que no todos los laboratorios pueden tener acreditada la norma ISO/IEC 17025, más aún por cada analito. Un ejemplo son los laboratorios de muchas Autoridades Nacionales Regulatorias. Esto encarecería el proceso, que justamente pretende evitar costos extra. Sugerimos se solicite que los laboratorios sigan los lineamentos de la norma ISO/IEC 17015, sin necesidad de estar acreditados La opción de formar un cluster de laboratorios, con eje en uno que posea dicha acreditación, entendemos no es válida dado que implica el traslado de los analitos en las condiciones de temperatura indicadas.	**AgroCare Latinoamérica**
11. Comentario de Chile:Si cada uno de los MR que un laboratorio posee son acreditados por ISO 17034 y se prepara la solución madre correspondiente y luego son preparados en mezcla, cumpliendo con todos los requisitos de trazabilidad según ISO 17025. ¿Por qué solo se puede evaluar la estabilidad de una mezcla adquirida de un productor de materiales de referencia (PMR) según el enfoque 3 y no la mezcla que es preparada en un laboratorio de análisis que cumple con ISO 17025? Se sugiere considerar en el enfoque 3, la posibilidad de evaluar las mezclas que sean preparadas en laboratorios de análisis,considerando que existen laboratorios que preparan sus propias mezclas para el análisis de plaguicidas a partir de MR individuales.	**Chile**
11. The stability of mixtures of RMs may be evaluated under these guidelines ~~only if~~ include the ~~mixture is~~ standard mixture purchased from the ~~RMP~~RMP as well as the standard mixture prepared by pesticide residues laboratories with ISO/IEC 17025 accreditation by using RMs purchased from RMPs, who can certify the purity and stability of each of the individual components. Refer to the 1st comment above.	**Singapore**

COMMENT	MEMBER / OBSERVER
~~11. The stability of mixtures of RMs may be evaluated under these guidelines only if the mixture is purchased from the RMP, who can certify the purity and stability of each of the individual components~~. The RMs shall be procured from an RMP accredited as per ISO 17034 to ensure analytical traceability or from a National Metrology Institute recognized by peers or designated by countries. The United States proposes swapping the order of criteria 11 and 12 for clarity.	**USA**
~~12. The RMs shall be procured from an RMP accredited as per ISO 17034 to ensure analytical traceability or from a National Metrology Institute recognized by peers or designated by countries.~~ The stability of mixtures of RMs may be evaluated under these guidelines only if the mixture is purchased from the RMP, who can certify the purity and stability of each of the individual components.	**USA**
17. ISO Guide[4] may be referred for assessing the shelf-life of an RM Thailand would like to propose the correction of the reference document “ISO Guide4” to “ISO Standard4”.	**Thailand**
18. Para garantizar la validez de los protocolos de ensayo de la estabilidad y la pureza que se indican a continuación, se llevarán los registros gravimétricos del MR (abierto o sin abrir), tanto sólido como líquido, y de sus respectivas soluciones madre durante el almacenamiento antes y después de su uso en cada momento. Antes de registrar el peso, el recipiente debe alcanzar la temperatura ambiente y ser limpiado para eliminar cualquier humedad adherida. La exposición del MR y las soluciones madre a la temperatura ambiente y la luz será tan breve como sea absolutamente necesario~~.~~ **. La exposición del MR y las soluciones madre a la temperatura ambiente y la luz será tan breve como sea absolutamente necesario, limitando el tiempo para su manipulación; posteriormente considerar de manera rigurosa para su adecuada conservación y trazabilidad: condiciones de almacenamiento (temperatura, luz, humedad, tipo de recipiente), fecha de caducidad, concentración, solvente (cuando aplique), analista responsable, instrumentos de medición utilizados, periodicidad de uso y preparación de mezclas(si aplica).** Se somete a consideración incluir el texto "La exposición del MR y las soluciones madre a la temperatura ambiente y la luz será tan breve como sea absolutamente necesario, limitando el tiempo para su manipulación; posteriormente considerar de manera rigurosa para su adecuada conservación y trazabilidad: condiciones de almacenamiento (temperatura, luz, humedad, tipo de recipiente), fecha de caducidad, concentración, solvente (cuando aplique), analista responsable, instrumentos de medición utilizados, periodicidad de uso y preparación de mezclas(si aplica)."	**Mexico**
18. Comentario de Chile:Es posible que existan diferencias en el peso del material de referencia entre el almacenamiento y el nuevo uso, al respecto, ¿Existirá un criterio de aceptación para evaluar la diferencia en la gravimetría que se pudiera presentar durante el almacenamiento?	**Chile**

COMMENT	MEMBER / OBSERVER
18/19. La indicación de llevar registros gravimétricos y de las condiciones de almacenamiento es adecuada y debería considerarse un requisito esencial para cualquier estrategia de extensión de vida útil. Esto incluye: o Establecer y mantener cadenas de custodia para los MR y sus soluciones madre, garantizando la trazabilidad desde su recepción hasta su uso final. o Implementar sistemas de monitoreo continuo, como dataloggers y cartas de control, para documentar y evaluar el desempeño de los equipos de almacenamiento a lo largo del tiempo.	**AgroCare Latinoamérica**
19. La indicación de llevar registros gravimétricos y de las condiciones de almacenamiento es adecuada y debería considerarse un requisito esencial para cualquier estrategia de extensión de vida útil. Esto incluye: - Establecer y mantener cadenas de custodia para los MR y sus soluciones madre, garantizando la trazabilidad desde su recepción hasta su uso final. - Implementar sistemas de monitoreo continuo, como dataloggers y cartas de control, para documentar y evaluar el desempeño de los equipos de almacenamiento a lo largo del tiempo.	**Argentina**
19/20. Humidity Monitoring (Paragraphs 19 and 20) Brazil seeks clarification on the reasoning behind the recommendation to monitor humidity during solution preparation. We point out that humidity typically impacts measurements only in specific cases (e.g., gravimetric verifications of pipettes or volumetric glassware). In most laboratories, particularly during the preparation of stock or working solutions, humidity is not a standard monitored parameter, unless the procedure involves hygroscopic materials. We respectfully request further explanation or scientific references to justify its inclusion.	**Brazil**
Criteria for storage conditions for pesticide reference materials and their stock solutions (paragraphs 20-22)	
According to the proposal of the European Union regarding the storage temperature condition of RM that could be extend its shelf-life, we are of the view that any provided information shall be based on scientific evidence and ensure that it is applicable to all RMs. Furthermore, we suggest it be clearly specified that storing RM at a temperature lower than that recommended by the RMP is a condition for unopened RMs only.	**Thailand**
~~**CRITERIA FOR**~~ **RECOMMENDED STORAGE CONDITIONS FOR PESTICIDE REFERENCE MATERIALS AND THEIR STOCK SOLUTIONS** Suggest changing to 'recommended conditions' rather than 'Criteria of Storage Condition'	**Singapore**
20. The storage conditions of RMs are specified by RMPs in the reference material documents, as ~~these~~ RMs are susceptible to degradation at high temperatures and other unfavorable environmental conditions. Environmental conditions (temperature and humidity, as appropriate) shall be recorded, monitored and controlled by the laboratory.	**USA**

COMMENT	MEMBER / OBSERVER
21. Storage Time Extension for Solutions (Paragraph 21) We agree that storage under more protective conditions (e.g., –18 °C) may extend the stability of pure, neat materials. However, it is important to note that storage at very low temperatures may diverge from the conditions specified by the RMP regarding the stability of CRMs in solution. In any case, we consider that the clause: "as long as these conditions do not contradict those indicated in the reference material document by the RMP" appropriately signals the need to assess each case individually.	**Brazil**
21. Si un laboratorio mantiene el MR en mejores condiciones de almacenamiento, es decir, protegen más que las recomendadas por el PMR (a temperatura más baja que la recomendada sin exposición a la luz y la humedad, **el tiempo para su manipulación y periodicidad de uso** etc.), el grado de deterioro del MR se reduce considerablemente siempre que esas condiciones no contradigan las indicadas por el PMR en el documento de información del material de referencia. En tales condiciones, la fecha de caducidad recomendada por el PMR puede prolongarse según corresponda para un MR hasta una fecha que permita el almacenamiento hasta 10 años o mientras la pureza mencionada en el documento del material de referencia se mantenga bien (≤ ±10 %) (SANTE[5], 2024). Otro estudio reveló que la estabilidad de los patrones de referencia del plaguicida alcanza hasta 15 años o la de la solución madre hasta 10 años[1,2]. Se somete a consideración la modificación del texto, para quedar como sigue: Si un laboratorio mantiene el MR en mejores condiciones de almacenamiento, es decir, protegen más que las recomendadas por el PMR (a temperatura más baja que la recomendada sin exposición a la luz, humedad, el tiempo para su manipulación y periodicidad de uso etc.), el grado de deterioro del MR se reduce considerablemente siempre que esas condiciones no contradigan las indicadas por el PMR en el documento de información del material de referencia. En tales condiciones, la fecha de caducidad recomendada por el PMR puede prolongarse según corresponda para un MR hasta una fecha que permita el almacenamiento hasta 10 años o mientras la pureza mencionada en el documento del material de referencia se mantenga bien (≤ ±10 %) (SANTE5, 2024). Otro estudio reveló que la estabilidad de los patrones de referencia del plaguicida alcanza hasta 15 años o la de la solución madre hasta 10 años 1,2.	**Mexico**
21. If a laboratory maintains the RMs at ~~better~~ storage ~~conditions, i.e.,~~ conditions more protective than those recommended by the RMPs (i.e., temperature lower than recommended without exposure to light and moisture, etc.), the rate of degradation of the RMs is significantly minimized as long as these conditions do not contradict those indicated in the reference material document by the RMP. Under such conditions, the expiry date as recommended by the RMPs may be extended as appropriate for an RM by a date allowing for storage of up to 10 years or as long as the purity mentioned in the reference material document holds good (≤ ±10%) (SANTE[5], 2024). Another study revealed the stability of pesticide reference standards for up to 15 years or in-stock solutions for up to 10 years[1,2].	**USA**
22. Los aspectos de almacenamiento en un recipiente adicional exterior, y el cuidado de abrirlos una vez que se llegue a temperatura ambiente deben enfatizarse, por ejemplo, en una "nota al pie". Muchos MR vienen en recipientes que pueden no asegurar la hermeticidad a temperaturas sub-ambientes, especialmente a -18°C (por ejemplo, dilatación diferencial de los materiales del frasco). La sugerencia de un tubo exterior hermético debe enfatizarse y de ser posible, entregar más detalles, como tipo de cierre (contratapa, "O" ring, etc.). No aconsejamos el uso de bolsas, dado que la experiencia muestra que estas no son suficientemente herméticas. Otra nota debería enfatizar la necesidad de asegurar la apertura del frasco a temperatura ambiente, dado que de lo contrario podría entrar humedad al mismo.	**Argentina**

COMMENT	MEMBER / OBSERVER
22. 1. Clarification Regarding Volumetric Flasks (Paragraph 22) We acknowledge that the updated version no longer refers explicitly to “volumetric flasks” as preferred containers for storage, and we consider this a positive improvement. However, we recommend adding a clear statement discouraging the use of volumetric flasks for storage, to avoid future misinterpretations, as these flasks are not designed to be airtight or to withstand extreme temperature conditions. The sentence “Exposing glassware to extreme temperatures should be avoided” could implicitly refer to this issue, but a more explicit clarification would be welcome. Suggested addition: Volumetric flasks should not be used for storage purposes, especially under refrigerated or frozen conditions, due to the risk of leakage or contamination. 2. Justification for Sealed Tubes/Pouches (Paragraph 22) While we understand the recommendation to place vials in sealed pouches or tubes to avoid contamination, we note that if reference materials are already provided in hermetically sealed containers, this additional step may not be necessary. However, we recognize that this recommendation may serve as an added precaution and does not negatively impact the overall guidance.	**Brazil**
22. To avoid any cross-contamination or degradation of RMs, the vials can be placed in an airtight capped tube/sealed pouch (made of suitable polypropylene or high-quality plastic material) and immediately stored in the freezer/refrigerator at conditions more protective than those recommended by RMPs, preferably at subzero temperature. The stock solutions must also be stored in airtight capped glassware or any other suitable ~~material~~ type of vessels as specified by the RMP. Storage conditions shall be controlled and monitored with appropriately calibrated equipment and ~~controlled and~~ recorded. Exposing glassware to ~~extreme~~ elevated temperatures should be avoided.	**Singapore**
22. To avoid any cross-contamination or degradation of RMs, the vials can be placed in an airtight capped tube/sealed pouch (made of suitable polypropylene or high-quality plastic material) and immediately stored in the freezer/refrigerator at conditions more protective than those recommended by RMPs, preferably at subzero temperature. The stock solutions must also be stored in airtight capped glassware or any other suitable material as specified by the RMP. Storage conditions shall be ~~monitored~~ monitored, controlled and recorded with appropriately calibrated ~~equipment and controlled and recorded~~equipment. Exposing glassware to extreme temperatures should be avoided.	**USA**
22. Los aspectos de almacenamiento en un recipiente adicional exterior, y el cuidado de abrirlos una vez que se llegue a temperatura ambiente deben enfatizarse, por ejemplo en una “nota al pie”. Muchos MR vienen en recipientes que pueden no asegurar la hermeticidad a temperaturas subambientes, especialmente a -18°C (por ejemplo, dilatación diferencial de los materiales del frasco). La sugerencia de un tubo exterior hermético debe enfatizarse y de ser posible, entregar mas detalles, como tipo de cierre (contratapa, “O” ring, etc). No aconsejamos el uso de bolsas, dado que la experiencia muestra que estas no son suficientemente herméticas. Otra nota debería enfatizar la necesidad de asegurar la apertura del frasco a temperatura ambiente, dado que de lo contrario podría entrar humedad al mismo.	**AgroCare Latinoamérica**

COMMENT	MEMBER / OBSERVER
Analytical protocol for monitoring the stability and purity of pesticide reference materials and individual stock solutions (paragraphs 23-26)	
PROTOCOLO ANALÍTICO PARA REALIZAR UN SEGUIMIENTO DE LA ESTABILIDAD Y LA PUREZA DEL MATERIAL DE REFERENCIA DE PLAGUICIDAS Y SOLUCIONES MADRE INDIVIDUALES CONSIDERACIONES ADICIONALES PARA TODOS LOS ENFOQUES Verificación de pureza de pico (UV o MS): - Descripción: Se comprueba que el pico del analito no esté contaminado con degradantes coeluidos. - Ventajas: * Aumenta la confiabilidad del análisis. * Detecta degradación invisible a nivel de área de pico. -Inconvenientes: * Requiere DAD o MS en modo adecuado. * Puede no detectar degradantes con espectros o m/z similares. Alícuotas congeladas y selladas al vacío: - Descripción: Fraccionamiento del MR al recibirlo y conservación bajo condiciones controladas. - Ventajas: * Reduce exposición a humedad, luz y temperatura. * Menor variabilidad entre usos. -Inconvenientes: Riesgo si no se realiza correctamente el sellado Modelado de tendencia de estabilidad: - Descripción: Registro gráfico de la desviación de pureza en el tiempo. - Ventajas: *Permite prever la caducidad real. *Facilita decisiones objetivas sobre descarte. -Inconvenientes: Puede ser afectado por cambios instrumentales si no se normaliza. Clasificación de riesgo del MR - Descripción: Asignación de riesgo bajo, medio o alto según la susceptibilidad del MR. - Ventajas: * Optimiza el uso de recursos analíticos. * Justifica distinta frecuencia de control. -Inconvenientes: Requiere criterio técnico y conocimiento previo del compuesto Viales prellenados y sellados para soluciones madre: - Descripción: Preparación de soluciones en condiciones óptimas, selladas y almacenadas sin manipulación frecuente. - Ventajas: * Mayor estabilidad. * Menor riesgo de contaminación o evaporación. -Inconvenientes: Necesita equipamiento y protocolo de preparación	**Argentina**

COMMENT	MEMBER / OBSERVER
23. Three analytical approaches may be considered for monitoring the stability and purity of individual ~~RMs and their~~ RMs, RM stock ~~solutions~~ solutions, and ~~mixed pesticide~~ RM ~~standards and~~ mixtures for the purpose of extending their use beyond the expiry date~~, provided their purity is proven acceptable~~.	**USA**
24. Esta estrategia es la más directa, confiable y ampliamente aceptada. Requiere contar con un MR nuevo para realizar la comparación, lo que limita su aplicabilidad cuando se busca evitar la compra de nuevos estándares. Sin embargo, si se dispone del nuevo lote, permite validar el anterior con un alto grado de certeza.	**Argentina**
24. In Approach 1, the stability of new (or unexpired) and old (or expired) RMs is determined simultaneously, ~~and it~~ which is applicable for individual neat standards and their related stock solutions. The comparisons of peak area shall be ~~run under repeatability conditions and mitigate~~ based on averaged values from repeated runs, which mitigates other sources of variation in instrument response~~, by averaging the values of replicate measurements~~. Alternatively, an internal standard (IS) may be used to compare the peak area ratio of new (or unexpired) and old (or expired) RMs. If the deviation (in peak area) after expiration date indicated by RMP is found within ±10%, or alternatively the peak area ratio deviation is within ±10%, the analyte in the RM is considered at an acceptable ~~and, therefore,~~ level and can therefore continue to be ~~considered for continued use~~ used as a valid RM. For neat standards and stock solutions, monitoring of stability & purity may be continued regularly up to a maximum of 10 years (SANTE) provided the deviation in purity remains acceptable[1,2,6]. Here, a new (or unexpired) RM would be required ~~for~~ throughout the period of comparison.	**Singapore**
24. In Approach 1, the stability of new (or unexpired) and old (or expired) RMs is determined simultaneously~~, and it is applicable for individual neat standards and their related stock solutions~~. The comparisons of peak area shall be run under repeatability conditions and mitigate other sources of variation in instrument response, by averaging the values of replicate measurements. Alternatively, an internal standard (IS) may be used to compare the peak area ratio of new (or unexpired) and old (or expired) RMs. If the deviation (in peak area) ~~after expiration is found within ±10%, or alternatively~~ between the ~~peak area ratio deviation~~ old (expired) RM and the reference RM is found within ±10%, the analyte in the old (expired) RM is acceptable and, therefore, can be considered for continued use as a RM. For neat standards and stock solutions, monitoring of stability & purity may be continued regularly up to a maximum of 10 years (SANTE) provided the deviation in purity from the original RMP remains acceptable[1,2,6]. Here, new (or unexpired) RM would be required for comparison~~.~~. Approach 1 is applicable for individual neat standards and their related stock solutions. Moved the sentence from line 1 to the bottom to emphasize the applicability. Perhaps underline. Added "from the original RMP" to indicate that users should not accrue a 10% deviation year over year	**USA**

COMMENT	MEMBER / OBSERVER
25. Sugerimos especificar las características de un PI para este uso 1. Alta estabilidad en condiciones normales y de almacenamiento prolongado: - Idealmente, no sensible a la luz, ni al oxígeno, ni a la humedad. - No volátil ni susceptible a hidrólisis u oxidación. 2. No higroscópico: - Evita variaciones de masa y concentración por absorción de humedad ambiental durante la preparación de soluciones. 3. Químicamente diferente del analito, pero: - Con respuesta similar en el detector (ej. UV, FID, MS). - Que no interfiera cromatográficamente 4. Accesible y económico: - Que esté disponible en grado analítico o p.a. (pureza ≥99%). - Que pueda comprarse en cantidades grandes, para evitar cambios de lote. No presente en las matrices reales, para que no interfiera en análisis de muestra.	**Argentina**
25. In the comments replies on Draft II rated to the implementation of Approach III for Mixture of standards we received the following answer "Approach 3 has been revised for clarity and is now aligned with Approach 1." Nevertheless, the approach stated in the document does not resemble the original proposed, we would like to know why it was changed and which were the bases to support that change. Approach III of the Draft II document it's not significantly different from Approach I. In the comments replies on Draft II rated to the implementation of Approach III for Mixture of standards we received the following answer "Approach 3 has been revised for clarity and is now aligned with Approach 1." The proposed approach does not imply a comparation of an "old" and "new" RM. Approach III is based on a classic stability study under intermediate conditions of measurement (ISO 33405). This study compares the same RM over time and does not require other "new" RM to be compared with. We kindly suggest reconsidering the description of Approach 3 and implementing the following description. "In Approach 3, whenever a new (or unexpired) RM is procured by any laboratory, its signal stability is monitored periodically before and after expiry using the same analytical conditions as mentioned in the reference material document. Here, new (or unexpired) RM need not be procured. An unexpired IS of any pesticide RM, appropriate for the method is used to account for any change in the response of the equipment. Here the peak area of the analyte (or alternatively the peak area ratio is) is plot against storage time. Next a linear regression analysis it's performed to test for significant changes in the area (or area ratio) of the analyte (as per classic stability study under ISO 33405). If the regression analysis indicates that the data does not fit a straight line the analyte in the RM is acceptable and, therefore, can be considered for continued use as a RM. The proposed Approach 3 its signally different from Approach 1 and 2, which bring a new tool for the laboratories to extend the validity of its RMs.	**Colombia**

COMMENT	MEMBER / OBSERVER
25. In Approach 2, whenever a new (or unexpired) RM is procured by any laboratory, its purity is monitored periodically before and after expiry using the same analytical conditions as mentioned in the reference material document. Here, new (or unexpired) RM need not be procured. An unexpired IS of any pesticide RM, appropriate for the method is used to account for any change in the response of the equipment. ~~This approach applies only to neat RMs accompanied by reference material documents.~~ As the analyte is spiked with the IS, the selection of the IS should be based on previous experience that shows a good stability over the expected storage time. The IS should further show a good measurement behavior and should not interfere with the measurement of the tested analyte. This approach applies only to neat RMs accompanied by reference material documents. Please explain what "good measurement behavior" means.	**USA**
26. Su correcta implementación es compleja y exige alta competencia técnica, ya que implica evaluar simultáneamente varios analitos en presencia de posibles degradantes y componentes de matriz. Esto requiere una separación cromatográfica robusta y métodos con capacidad de resolución suficiente para minimizar el riesgo de coeluciones. Aunque esta estrategia puede optimizar tiempo y recursos en laboratorios con experiencia en métodos multiresiduo, no es recomendable en entornos con instrumentación o validaciones limitadas.	**Argentina**
26. Approach 3 is similar to Approach 1 wherein the stability of new (or unexpired) and old (or expired) RM is determined simultaneously and is applicable to mixed pesticide RM standards. As in approach 1, the comparisons of peak area of each pesticide RM in the mixture shall be ~~run under repeatability conditions and mitigate~~ based on averaged values from repeated runs, which mitigates other sources of variation in instrument response~~, by averaging the values of replicate measurements~~. Alternatively, an internal standard (IS) may be used to compare the peak area ratio of each RM pesticide in new (or unexpired) and old (or expired) mixture. If the deviation (in peak area) after expiration is found within ±10%, or alternatively the peak area ratio deviation is within ±10%, for each pesticide RM in the mixture, the analyte in the RM is considered at an acceptable ~~and, therefore,~~ level and can therefore continue to be ~~considered for continued use~~ used as a valid RM.	**Singapore**
26. Approach 3 is similar to Approach 1 ~~wherein the stability of new (or unexpired)~~ and ~~old (or expired) RM~~ is ~~determined simultaneously and is~~ applicable to mixed pesticide RM standards. ~~As in approach 1~~In this approach, ~~the comparisons of~~ deviation (in peak ~~area of each pesticide RM in the mixture shall~~ area) must be ~~run under repeatability conditions and mitigate other sources~~ determined for each component of ~~variation in instrument response, by averaging~~ the ~~values of replicate measurements. Alternatively, an internal standard (IS) may be used to compare the peak area ratio of each RM pesticide in new (or unexpired) and old (or expired)~~ mixture. If ~~the deviation (in peak area)~~ after ~~expiration is found within ±10%, or alternatively~~ the ~~peak area ratio deviation is~~ expiry date all components are found within ~~±10%, for each pesticide RM in~~ ±10% of the ~~mixture~~reference RM, the analyte in the RM is ~~acceptable and~~acceptable, and therefore, can be considered for continued use as a RM. If any of the components do not meet the ±10% criterion, the mixture may not be used as an RM. For clarity, if extension of RM mixtures is appropriate. Could also be combined under approach 1.	**USA**

COMMENT	MEMBER / OBSERVER
Approach 1: Comparing the stability of old (or expired) and new (or unexpired) pesticide reference standards; applicable to neat standards of reference materials and related stock solutions (paragraphs 27-33)	
Approach 1: Comparing the stability of old (or expired) and new (or unexpired) pesticide reference ~~standards; applicable~~ standards (applicable to neat standards of reference materials and related stock ~~solutions~~ solutions)	**Singapore**
27. Prepare a fresh stock solution of the old (or expired) and new (or unexpired) RM standard of the appropriate concentration~~., Appropriate concentration will depend~~ depending on the response of the RM in the detector. Generally, for HPLC[1]-DAD[2]/GC[3]-FID[4], a good response is obtained between 10 mg L^{-1} to 100 mg L^{-1}. For single quadrupole GC-MS[5] or LC[6]-MS, the appropriate concentration typically ranges from 1 to 5 mg L^{-1}, while for triple quadrupole GC-MS/MS or LC-MS/MS, 0.1 to 0.5 mg L^{-1} or lower concentration may be more appropriate to avoid signal saturation.	**Singapore**
27. We noted that appropriate concentration specified for detector do not cover the range of 0.5 mgL-1 to 1 mgL-1 and of 5 mgL-1 to 10 mg/l. To improve practical clarity, we recommend setting clear criteria for these ranges.	**Thailand**
29. Method 1 (Peak Area Comparison): Inject standard solutions of the old (or expired) and new (or unexpired) individual RMs prepared from the stock solution at the same concentration into the instrument and record the peak area. It is recommended that the injection sequence ~~contain~~ contains at least five replicates of new (or unexpired) and old (or expired) standards and should be alternating to minimize the drifting of signal response in the course of measurement. Calculate the mean value of the peak area for the old (or expired) and new (or unexpired) RM of the five replicates. The %RSD of the replicate measurements should be ≤ ±10%. Calculate the % deviation in average peak area of the old (or expired) and new (or unexpired) standard solutions using the formula below given. The mean value from the new (or unexpired) solution is taken to be 100% and is also used as a basis for calculating the percentage difference.	**Singapore**
30. Method 2 (Peak Area Ratio Comparison): Spike ~~a different~~ another RM (inert and unexpired) as an IS into the standard solutions of the old (or expired) and new (or unexpired) RMs prepared from the stock solution at the same concentration. Inject the solutions and record the peak area of the RM and the IS, perform a minimum of five replicate measurements, and calculate the average ratio of RM area to IS area for the old (or expired) and new (or unexpired) RMs with %RSD ≤ 10%. The IS peak should have a similar abundance to the RM being verified, and it should not interfere with the analysis of the target RM in terms of either retention time or molecular weight (m/z). Calculate the % deviation using the below given formula:	**Singapore**
30. In Method 2 of Approach 1: Comparing the stability of old (or expired) and new (or unexpired) pesticide reference standards; applicable to neat standards of reference materials and related stock solutions, paragraph 30, we suggest including the phrase from Method 1 "It is recommended that the injection sequence contain at least five replicates of new (or unexpired) and old (or expired) standards and should be alternated to minimize signal response drift during the measurement." We consider that the inclusion of the internal standard does not entirely prevent signal drift that could affect the analysis. Furthermore, we understand that it would simplify the document if the procedure for both methods in Approach 1 were generally the same.	**Uruguay**

COMMENT	MEMBER / OBSERVER
32. El patrón viejo (o caducado) se comparará con el patrón nuevo (o no caducado) a intervalos regulares de al ~~menos una vez~~ menos **dos veces** al año, siempre que se mantengan las condiciones de almacenamiento recomendadas. Se somete a consideración modificar la periodicidad de los intervalos regulares, para quedar como sigue: El patrón viejo (o caducado) se comparará con el patrón nuevo (o no caducado) a intervalos regulares de al menos dos veces al año, siempre que se mantengan las condiciones de almacenamiento recomendadas.	**Mexico**
32. The old (or expired) standard shall be compared with the new (or unexpired) standard at regular intervals of initially at least every three months and then be extended to at least once a ~~year~~year after the establishment of the stability characteristics of the concerned RM, provided the recommended storage conditions are maintained. Singapore is of the view that when an RM's stability profile is not yet established, the initial monitoring interval should be at least quarterly. This is because if the stability of an RM is found to have degraded by more than 10% after one year, the reliability of the test results released by the pesticide residues laboratory in the preceding months may be brought to question. This is a risk which every pesticide residues laboratory should avoid.	**Singapore**
Approach 2: Verification of purity of neat standards of pesticide reference materials during prolonged storage (not suitable for verification of stock solutions) (paragraphs 34-41)	
34. To verify the purity of the RM, a chromatographic assay shall be performed, preferably as per the analytical conditions mentioned in the reference material document by the RMP, with the capability of resolving and detecting the target analytes away from all of its potential impurities. If it is not feasible to match the exact conditions of the RMP, deviations should be documented and justified. Furthermore, if the deviation comes from the use of a different technique, the laboratory must guarantee that the technique has an equivalent or better sensitivity. RM purity is verified by comparing the purity (in terms of percent peak area) obtained through analysis with the purity mentioned in the reference material document. Suggest including the additional text since we are determining the purity based on percentage of peak area of the RM.	**Singapore**
34. To verify the purity of the RM, a chromatographic assay shall be performed, preferably as per the analytical conditions mentioned in the reference material document by the RMP. If it is not feasible to match the exact conditions of the RMP, deviations should be documented and justified. Furthermore, if the deviation comes from the use of a different technique, the laboratory must guarantee that the technique has an equivalent or better ~~sensitivity~~sensitivity and specificity. RM purity is verified by comparing the purity (in terms of percent peak area) obtained through analysis with the purity mentioned in the reference material document. To ensure that the are no interferences	**USA**

COMMENT	MEMBER / OBSERVER
35. Prepare a fresh stock solution of the new (or unexpired) neat standards of RMs and IS (a different unexpired RM) of appropriate concentration in a suitable solvent. The IS solution should be prepared in the same solvent in which the stock solution is prepared to consider any background interference that may be present. Appropriate concentration will depend on the response of the RM using the selected detection ~~method; please see~~ method (see paragraph 27 of Approach 1 for suggested concentration ~~ranges~~ranges).	**Singapore**
35. We would like to propose that three minimum replicates might be preferable to five replicate measurements. Rationale: When the instrument is ready to be used, deviations from sample injection should not have a significant effect. If there is a significant difference in detector response, this indicates troubleshooting, and all measurements must be repeated.	**Indonesia**
36. Prepare the standard solution of the RM from the stock solution and analyze it through the instrument (HPLC-DAD, HPLC-UV, GC-FID, LC-MS, GC-MS in full scan mode, or qNMR) as per the analytical conditions mentioned in the reference material document. The ~~percent~~ percentage of peak area obtained through the software of the instrument ~~while carrying out the analysis~~ is recorded as ~~percent~~ purity. Inject a blank solution of the same solvent in which the stock solution is prepared prior to this to ~~consider~~ check any background interference that may be present. A minimum of five replicate measurements shall be performed to obtain a mean value of ~~percent~~ purity, and the %RSD of the replicates should be ≤ 10%. The instrument shall be calibrated as per the ~~conditions~~ procedures and criteria recommended by the manufacturer.	**Singapore**
38. Comentario de Chile:En fórmula “(área media del porcentaje de pico del patrón puro … debería decir % de pureza media determinada del patrón.	**Chile**
40. Repeat the same procedure at regular intervals of initially at least every three months and then extended to once a year when the stability characteristic of the concerned RM is established using a freshly prepared solution of the RM and compare with the freshly prepared solution of the unexpired IS, particularly before and after the RM's expiry, to monitor its stability and purity during prolonged storage and obtain % deviation in the ratio of peak area. Suggest including the additional text due to rationale stated earlier under para 32.	**Singapore**
40. Thailand is of the view that the calculation formula should be divided by the "mean peak area ratio of RM before expiry and IS" rather than that of RM after expiry. we noticed that all of other equations compare the deviation to the value from the RM before expiry or the new RM.	**Thailand**
41. After the expiry date of the ~~RM~~RM as indicated by its RMP, if the mean value of percent purity in terms of percent peak area obtained for the RM and the reference value (as obtained from reference material document) do not differ by more than ±10% (the % deviation of less than or equal to ±10%) and the deviation (%) in the ratio of peak area for the RM compared to the internal standard is ≤ ±10%, the RM may be considered suitable for continuing use as a valid RM in the laboratory.	**Singapore**

COMMENT	MEMBER / OBSERVER
Approach 3: Verification of stability of mixed pesticide RM standard solutions during prolonged storage. (paragraphs 42-48)	
As approach 3 is nearly identical to approach 1, the United States suggests that approach 3 could be deleted and language addressing mixtures could be added to the above paragraphs of approach 1. This may simplify the guidelines for the reader.	**USA**
42. Suggested Wording Revision – Approach 3 (Paragraph 42 onwards) In Approach 3, the phrase: "Prepare a fresh stock solution of the new..." may cause confusion when applied to mixed reference standards (MRCs), which are often already in stock solution form. We recommend changing this to: "Prepare a fresh working solution of the new..." This change reflects common laboratory practice where mixed reference materials are diluted to working concentrations rather than being reconstituted into new stock solutions. Brazil hopes these contributions will support the refinement and clarity of the Guidelines. We reaffirm our appreciation for the valuable work of the drafting group and remain available to contribute further.	**Brazil**
42. In the comments replies on Draft II rated to the implementation of Approach III for Mixture of standards we received the following answer "Approach 3 has been revised for clarity and is now aligned with Approach 1." The proposed approach does not imply a comparation of an "old" and "new" RM. Approach III is based on a classic stability study under intermediate conditions of measurement (ISO 33405). This study compares the same RM over time and does not require other "new" RM to be compared with. The general idea of this approach is to ensure that the concentration or the signal measure of the RM does not change over time, even after the expiration date. We kindly suggest adding the steps mentioned in the previous comments Repeat the same procedure at regular intervals of at least once a year using a new stock solution of the RM, particularly before and after the RM's expiry, to monitor its stability and purity during prolonged storage. The new proposed Approach 3 is aligned to the classic stability studies described in ISO 33405. Witch is an Approach commonly used in the Production of Reference Materials	**Colombia**
42. This approach has been aligned with Approach 1. Prepare a fresh stock solution of the new (or unexpired) and old (or expired) mixed pesticide RM standard of appropriate concentration in a suitable solvent. Appropriate concentration will depend on the response of the RM using the selected detection ~~method; please see~~ method (see paragraph 27 of Approach 1 for suggested concentration ~~ranges~~ranges).	**Singapore**

COMMENT	MEMBER / OBSERVER
42. The stability and purity of RMs purchased as a mixture from the RMP may be evaluated using Approach 1. Evaluate each pesticide RM in the mixture following the protocol for Approach 1, either method 1 or method 2. ~~This approach has been aligned with Approach 1.~~ Prepare a fresh stock solution of the new (or unexpired) and old (or expired) mixed pesticide RM standard of appropriate concentration in a suitable solvent. Appropriate concentration will depend on the response of the RM using the selected detection method; please see paragraph 27 of Approach 1 for suggested concentration ranges.	**USA**
43. After the expiry of the RM, repeat the procedure as described in paragraph 45 and create a graph of the area ratio of each component against time.	**Colombia**
43. Analyze the standard solution of the old (or expired) and new (or unexpired) RM mixture on a proper instrument (HPLC-DAD, HPLC-UV, GC-FID, LC-MS, GC-MS in full scan mode, GC-MSMS/LC-MSMS in MRM mode or qNMR) as per the analytical conditions mentioned in the reference material document and record the peak area. Either of the two methods described below can be employed. Suggest adding GC-MSMS and LC-MSMS under MRM mode here since they are more effective for quantifying the concentrations of individual components in a standard mixture. This is very important point since the standard mixtures use in multi-residues methods very often may contain a few hundreds of pesticides, for which it is very difficult to use HPLC-DAD, HPLC-UV, and definitely not GC-FID methods for stability and purity check.	**Singapore**
43. In Approach 3: "Verification of stability of mixed pesticide RM standard solutions during prolonged storage," paragraph 43, we suggest indicating that the LC-MS is operating in "full scan mode" in the instrument list. We believe that, as with the GC-MS, it is necessary to clarify the mass spectrometer acquisition mode. Within Approach 3 itself, we consider that the comparison of different compounds in mixtures can also be performed using LC-MS/MS and GC-MS/MS. We understand that many laboratories routinely operate in MS/MS mode, and in those cases, it is the most reliable way to compare mixtures. Furthermore, we believe that stability determinations in Approach 3 should be allowed to proceed in the same manner as in Approach 1.	**Uruguay**
44. Perform a linear regression analysis and determine if the model fits the data correctly.	**Colombia**
44. Method 1 (Peak Area Comparison): Inject standard solutions of the old (or expired) and new (or unexpired) mixed pesticide RM prepared from the stock solution at the same concentration into the instrument and record the peak area of each pesticide RM in the mixture. It is recommended that the injection sequence ~~contain~~ contains at least five replicates of new (or unexpired) and old (or expired) standards and should be alternating to minimize the drifting of signal response in the course of measurement. Calculate the mean value of the peak area of the five replicates for the old (or expired) and new (or unexpired) RM. The same will be calculated for all the pesticide RMs in the mixture. The %RSD of the replicate measurements should be ≤ 10%. Calculate the % deviation in average peak area of each pesticide RM in the old (or expired) and new (or unexpired) standard solutions of the mixture using the formula below given:	**Singapore**

COMMENT	MEMBER / OBSERVER
45. If the regression analysis indicates that the data do not fit a straight line (R-Squared under 0.8 and p-value > 0.05), it can be established that storage time has not been a factor contributing to a change in the obtained response. Therefore, the RM may be considered suitable for continuing use in the laboratory.	**Colombia**
46. Repeat the same procedure at regular intervals of at least once a year using a new stock solution of the RM to monitor its stability and purity during prolonged storage.	**Colombia**
46. New proposed paragraph to be added: If any of the RMs in the mixture (as obtained from the above Method 1 or Method 2) shows a deviation of > ±10% relative to the product information sheet provided by the RMP, the old (or expired) pesticide RM mixture IS NOT suitable for continued use and should be discarded.	**USA**
46. If ~~the % deviation for~~ every pesticide RM in the mixture (as obtained from the above Method 1 or Method 2) shows a deviation of ≤ ~~±10%~~±10% relative to the product information sheet provided by the RMP, the old (or expired) pesticide RM mixture may be considered suitable for ~~continuing~~ continued use.	**USA**
47. The old (or expired) mixed pesticide RM standard shall be compared with the new (or unexpired) mixed pesticide RM standard at regular intervals of at least ~~twice a year~~quarterly, provided the recommended storage conditions are maintained. Suggest change the interval to 'at least quarterly' since standard mixture is in solution of much lower concentration, which is more prone to degradation.	**Singapore**
48. To monitor the stability of the mixed pesticide RM standard over time, a plot of % deviation vs. time of monitoring may help identify and predict the deviation in stability with time. ~~To monitor the stability of the mixed pesticide RM standard over time, a plot of % deviation vs. time of monitoring may be made, which would help identify and predict the deviation in stability with time.~~	**USA**
ANNEX	
Mixture of Reference Material This term should be used consistently throughout the document. The terms "mixtures of pesticide standards", "mixture of RMs", "RM mixture of pesticides", and "RM mixture" are also used and should be consolidated.	**USA**