Council for International Organizations of Medical Sciences

First meeting of the CIOMS Working Group (WG) XVII on Long-term safety of medicinal products

2-3 December 2025, Geneva, Switzerland, hybrid meeting

Minutes

Overview:

Summary

The CIOMS Working Group (WG) XVII on Long-term Safety of Medicinal Products held its first meeting in Geneva, Switzerland, on 2-3 December 2025, with participants attending both in person and virtually. The purpose of the meeting was to allow members to share perspectives, identify key gaps, and clarify how the topic of long-term safety should be approached. Discussions highlighted the diversity of long-term safety issues across different product types, populations and mechanisms of action, and the need for a structured conceptual and methodological framework. Two subgroups were established to begin developing the initial building blocks of the WG's work. A virtual meeting is planned for late February or early March 2026, and the next in-person meeting is planned for late spring or early summer 2026, to review progress and further advance the draft framework.

Minutes of discussion

Day 1

Opening and welcome

- Stella Blackburn, CIOMS President, opened the session and welcomed the members to the first meeting of the CIOMS WG XVII. She noted that the start of a new CIOMS WG is an important moment, bringing together experts from different backgrounds to address areas where scientific, regulatory and practical gaps exist.
- She highlighted that the safety profile of a medicine is often still incomplete at the time of authorisation. While efficacy is usually well established, many safety issues, particularly those related to long-term use or delayed effects, can only be detected after wider and longer use. Risk management plans have improved the way benefits and risks are managed, but important uncertainties about long-term safety remain.
- She noted that long-term safety is a broad and complex topic, as reflected in the concept note, and that one of the Working Group's first tasks will be to clarify the scope and priorities of its work. Participants were encouraged to work towards the shared objective of producing guidance that supports patient safety and public health.
- Lembit Rägo, CIOMS Secretary General, added his words of welcome. He highlighted the importance of this WG in addressing emerging and unresolved challenges related to long-term safety of medicinal products, particularly in light of rapidly evolving therapeutic technologies.
- Lembit noted that several CIOMS Working Group reports had been published during the year:
    - WG XII report on Benefit-Risk Balance for Medicinal Products;
    - Report on Severe Cutaneous Adverse Reactions – SCAR;
    - WG XIV on Artificial Intelligence in Pharmacovigilance. (post-meeting comment: the WG XIV report was published on 4 December 2025). The report on the use of artificial intelligence in pharmacovigilance sets out general principles for the use of artificial intelligence, which are relevant not only to pharmacovigilance but also to other areas of product development and regulation.
- There are several ongoing CIOMS WGs (more information at https://cioms.ch/).
- Lembit also noted that CIOMS has increasingly used webinars to introduce newly published WG reports, and that this approach would be continued for future reports, including the outcome of Working Group XVII.
- Turning to the current WG, Lembit explained that the concept note provides direction and background but does not prescribe the final scope or structure of the work. The first meeting was therefore intended to allow participants to share perspectives, identify gaps and clarify how the topic of long-term safety should be approached.
- *Tour de table* was made to introduce participants to each other. For a list of participants see Annex 1.
- Agenda was adopted.
- Kateriina was rapporteur.

Scope of the WG and Initial Reflections

- Lembit invited participants to provide their perspectives on what "long-term safety" should mean in the context of this WG and what key gaps or challenges they saw from their professional experience.
- It was acknowledged that the concept note provided a broad framework, but that its purpose was to stimulate discussion rather than to define the scope in advance. Participants were encouraged to speak openly about where they saw current systems failing or where new guidance was needed.
- During the discussion it was recognised that long-term safety encompasses several distinct but related dimensions. These include adverse effects that occur after a long delay following exposure, effects that persist or become irreversible, effects that emerge after treatment has been discontinued, and effects that may manifest later in life or even in subsequent generations.
- The WG members noted that traditional pharmacovigilance systems were not designed to capture all of these dimensions effectively.

Interventions from participants: Regulatory perspectives

- Regulatory participants described the increasing complexity of assessing and managing long-term safety across a wide range of therapeutic modalities.

Emerging Therapies and Multigenerational Risk

- It was noted that advanced therapies, including gene-based and cell-based products, have fundamentally altered the landscape of long-term safety. Unlike small molecules, these products may permanently modify biological systems, raising questions about late-onset toxicities, genomic integration, reproductive effects, and potential multigenerational consequences.
- Examples were given of therapies administered early in life, where safety monitoring may need to extend into adolescence, adulthood, and potentially to offspring. In such cases, long-term safety could span decades and require innovative approaches to follow-up and data collection.

Limits of Traditional Safety Monitoring

- Participants emphasised that spontaneous adverse event reporting systems remain essential but are insufficient for capturing many long-term or delayed risks. These systems rely on clinical suspicion and reporting, which becomes increasingly unreliable as the temporal distance from exposure increases.
- Long-term safety therefore requires complementary data sources, including:
    - registries,
    - real-world data,
    - electronic health records,
    - and other longitudinal healthcare datasets.
- However, these sources come with their own limitations, including incompleteness, heterogeneity, and difficulties in linking exposure to outcomes.

Definition and Conceptual Clarity

- A strong need was expressed for clearer terminology. “Long-term safety” was seen to encompass very different situations:
    - long duration of exposure,
    - long latency to onset,
    - long persistence of harm,
    - or effects appearing after discontinuation.
- Without precise definitions, it becomes difficult to design appropriate monitoring strategies, regulatory requirements, or studies.

Vulnerable Populations

- Special attention was drawn to populations in whom long-term risks are particularly consequential, including:
    - paediatric populations, where organ maturation and development may be affected,
    - patients receiving lifelong or very early interventions,
    - and those with rare diseases where data are sparse.
- It was noted that long-term safety expectations may need to differ by population and by therapeutic context.
- While existing risk management frameworks allow long-term safety issues to be addressed, concerns were raised about the sustainability of some current approaches, particularly for very long follow-up periods. Questions were raised about who should be responsible for maintaining long-term registries and follow-up when products change ownership or companies no longer exist.

Industry Perspectives

- Industry participants broadly agreed with the challenges identified by regulators and highlighted additional operational and methodological issues.

Data Sources and Causality

- It was emphasised that spontaneous reporting alone cannot provide reliable insight into long-term safety, particularly for common background conditions such as cardiovascular disease. Distinguishing drug-related risk from background incidence becomes increasingly difficult over time.
- Industry representatives highlighted the need for:
    - clearly defined outcomes of interest,
    - systematic approaches to monitoring,
    - and access to alternative data sources capable of supporting causal inference.

Rare and Individualised Therapies

- With the growth of personalised and ultra-rare disease therapies, it was noted that traditional population-based pharmacovigilance becomes less applicable. When therapies are administered to very small numbers of patients, or even to single individuals, new models of safety monitoring are required.
- Participants suggested that disease registries, patient-level data, and international collaboration may be necessary to support meaningful long-term safety evaluation in these contexts.
- It was stressed that patient-reported information remains critical, particularly for long-term and quality-of-life-related outcomes. While new data sources are important, spontaneous and direct patient reporting should not be neglected.
- The need for patient consent and access to patient-level data was highlighted as a major constraint on long-term safety monitoring. Emerging technologies that allow dynamic consent and long-term data linkage were seen as potentially important tools.

Methodological and Scientific Considerations

- Participants across sectors discussed the need for more rigorous and forward-looking methodological frameworks for long-term safety.
- Key themes included:
    - the distinction between retrospective and prospective monitoring,
    - the use of real-world evidence and large healthcare databases,
    - the challenges of defining appropriate comparators,
    - and the need for methods capable of detecting rare, delayed, or multigenerational effects.
- The importance of aligning long-term safety evaluation with benefit–risk assessment was also emphasised. Participants noted that long-term risks must always be weighed against the benefits of treatment, particularly in serious or life-threatening diseases.

Structuring the Work of the Working Group

- Lembit emphasised the importance of moving from high-level discussion to a more structured framework. He noted that Working Groups that establish a draft table of contents early tend to be more effective, as it provides a concrete basis for discussion and refinement.
- He also stressed the need to bring order to the broad concept of long-term safety, describing it as a “single box” currently containing many very different types of risks and challenges. The WG was encouraged to think in terms of building blocks and conceptual structure, potentially differentiated by:
    - type of product,
    - mechanism of action,
    - population,
    - and scale of exposure.
- To enable deeper discussion, participants were divided into two mixed breakout groups (including representation from all stakeholders and both in-person and virtual attendees). Each group was tasked with identifying the potential “building blocks” of the WG’s future report, including:
    - key concepts,
    - possible chapters or sections,

  - and major thematic areas that should be addressed.

- It was explained that both subgroups would work on the same task independently, after which their outputs would be compared and integrated to create a more complete and balanced structure.

DAY 2

- Lembit Rägo welcomed participants back for the second day of the meeting and summarised the key conclusions from Day 1. He recalled that there had been broad consensus that the WG should move rapidly towards producing a first draft of the report using a shared drafting approach. Two drafting groups would therefore prepare the initial iteration, which would then be reviewed by the full WG.
- He reminded participants that the purpose of the first meeting was not to finalise technical positions but to establish a workable structure, shared understanding, and a realistic roadmap for the WG's work.
- Given the time of year and workload of members, it was acknowledged that immediate progress before the end of the year would be limited. It was therefore proposed that a virtual full-group meeting be scheduled for late February – early March to review progress on the first draft and determine next steps.
- An in-person meeting was tentatively proposed for late spring or early summer (likely May or June), recognising the heavy conference and travel schedules during that period. Participants were asked to indicate possible availability once proposed dates were circulated.
- Lembit also noted that CIOMS is open to holding meetings in different locations where appropriate logistical and local support can be provided. Participants were invited to suggest possible host organisations or venues, provided they could offer reasonable facilities.

Report-back from Breakout Groups

- Following the breakout discussions held at the end of Day 1, both subgroups reconvened in plenary to report on their conclusions regarding the conceptual structure and building blocks for the WG's future report.
- Although the two groups had worked independently, their outputs were largely complementary and converged around several core themes.

Conceptualisation of Long-term Safety

- Both subgroups agreed that "long-term safety" cannot be treated as a single homogeneous concept. Instead, it should be understood as a set of distinct but related dimensions, including:

  - The nature and duration of exposure, which may involve long-term treatment, repeated administration or a single, one-time administration (e.g. for advanced therapies)
  - Latency to onset (effects appearing long after exposure)
  - Persistence or irreversibility of adverse effects
  - Post-treatment effects**,** including those occurring after therapy has stopped
  - Intergenerational effects**,** including effects on reproduction or offspring

- It was agreed that any CIOMS guidance must explicitly separate and define these dimensions to avoid ambiguity and misinterpretation.

Population-specific Considerations

- Both groups emphasised that population matters for long-term safety and that different approaches are required for:
    - paediatric populations (including organ development and maturation),
    - pregnant patients and in-utero exposure,
    - adults receiving long-term therapy,
    - elderly populations,
    - and ultra-rare disease populations with very small numbers of exposed patients.
- Participants stressed that long-term safety expectations, monitoring methods and data needs should be stratified by population rather than applied uniformly.

Product and Mechanism-based Framework

- The subgroups agreed that mechanism of action is a key organising principle. Products that permanently alter biological systems (e.g. gene- and cell-based therapies) raise fundamentally different long-term safety questions from small molecules or traditional biologics.
- The Working Group therefore agreed that guidance should be structured around:
    - classes of products,
    - mechanisms of action,
    - and potential for biological persistence or modification.

Exposure and Scale of Use

- A further dimension highlighted was magnitude of exposure, recognising that:
    - products used in millions of people (e.g. vaccines) present challenges of signal detection against background rates,
    - while products used in tens or hundreds of patients require international pooling of data and bespoke registries.
- Long-term safety systems must therefore be proportionate to the scale of exposure.

Data Sources and Evidence Generation

- Both subgroups agreed that traditional spontaneous reporting is insufficient to address most long-term safety questions.
- The following sources were identified as essential components of future long-term safety systems:
    - disease and product registries,
    - electronic health records,
    - claims and administrative data,

  - real-world evidence platforms,
  - patient-reported outcomes,
  - and linked multi-database networks.

- The importance of data quality, interoperability, governance, patient consent, and the education of healthcare professionals on new therapies and their long-term safety risks was emphasised.

Methodological Framework

- Both groups stressed the need for a methodological framework that goes beyond passive surveillance and includes:

  - prospective planning at the time of product development,
  - predefined long-term safety objectives,
  - appropriate comparator strategies,
  - and use of modern pharmacoepidemiological methods.

- The subgroups also noted that long-term safety must be assessed within a benefit-risk context, particularly for serious and life-threatening diseases.
- The burden on patients, healthcare professionals and healthcare systems was recognised as a critical factor when designing long-term safety follow-up.
- The WG agreed that these subgroup outputs in a form of a merged Table of Contents would serve as the foundation for drafting and that the two drafting groups would now proceed to develop the first version of assigned sections for review at the next full meeting.

Way of working

- It was confirmed that CIOMS would provide practical support for subgroup meetings and, where needed, minute-taking support.
- Participants were encouraged to make use of subgroup meetings between plenary sessions in order to advance drafting and technical discussion.
- To ensure momentum and coordination, each subgroup was asked to nominate a lead who would:

  - help coordinate contributions,
  - convene subgroup meetings where necessary,
  - and serve as the main contact point for CIOMS support.

Lembit explained a few practical matters about the CIOMS WGs in general:

- Each CIOMS group finalises a guideline, usually in 2-4 years, which will be both in electronic and print formats. All CIOMS reports are free to be downloaded from the CIOMS website.
- The draft minutes from meetings will always be provided to the members to review and approve before being uploaded to the public WG page on the CIOMS website.
- Where WG members consent to meetings being recorded for the purposes for taking minutes, the recordings will not be used for any other purpose and will be deleted as soon as possible.

The WG reviewed a provisional table of contents for the future report and assigned sections to the two drafting groups.

It was agreed that:

- The introductory and background sections would be drafted later, once the substantive content of the report was clearer.
- Core technical chapters addressing long-term safety concepts, regulatory and methodological frameworks, and specific safety domains would be divided between the two groups for initial drafting.
- Some foundational chapters would be reviewed jointly to ensure conceptual alignment.

- The intention was not to produce final text, but rather a structured first draft that could be iteratively improved through full-group discussion.
- Participants were encouraged to engage actively once draft materials became available and to suggest relevant scientific literature or ongoing initiatives that could inform the WG's work.

- Participants were invited to share publications, guidelines and ongoing initiatives relevant to long-term safety.

Several members referred to:

- existing CIOMS guidance on signal detection,
- emerging literature on long-term safety and pharmacoepidemiology,
- and new work on artificial intelligence and pharmacovigilance.
- Lembit confirmed that CIOMS Secretariat would circulate relevant materials to the full group.

Next steps / next meeting

- Participants discussed the need for a shared digital workspace to support collaborative drafting and document sharing. It was acknowledged that security and access restrictions vary widely across organisations, making it difficult to identify a platform that works for all participants.
- Previous attempts in other WGs to establish shared platforms had often failed because some participants were unable to access them.
- It was therefore agreed to attempt a cloud-based shared workspace using a widely accessible platform, with the understanding that adjustments might be needed if access problems arose.
- The dates for the next full WG meeting will be researched, and a Doodle polls will be circulated.

Closing remarks

- Lembit thanked both the in-person and virtual participants, acknowledging the effort required to attend across time zones. He noted that the WG had made strong progress for a first meeting, having already established the initial conceptual structure and draft table of contents for the future report, and expressed confidence that the WG was well positioned to deliver a meaningful and high-quality outcome.

Subgroup 1 lead and members (listed in no particular order):

Sheetal (lead), Nadiya, Hussein, Yukiko, Khedidja, Nokuthula, Mahlodi, Mariette, Qun-Yin, Claudia, Esther, Pilar, Andrea, Wang.

Subgroup 2 lead and members (listed in no particular order):

Jean-Marie (lead), Leila, Andrea, Martin, Agnieszka, Christina, Leigh, Susan, Claire, Marie, Monica, Ian, Dirk.

Annex 1: List of participants

Attending in person

Samvel Azatyan (CIOMS), Stella Blackburn (CIOMS), Mariette Boerstoel-Streefland (Bristol Myers Squibb), Marie-Pierre Caby-Tosi (Moderna), Ian Douglas (London School of Hygiene & Tropical Medicine), Leigh Henderson (Medicines and Healthcare products Regulatory Agency), Jean-Marie Heim (Takeda), Martin Huber (Federal Institute for Drugs and Medical Devices, Germany), Nadiya Jirova (Health Canada), Susan Kaplan (Merck), Sheetal Khedkar (Johnson & Johnson), Hussein Laljee (Gilead), Leila Larbi (AbbVie), Andrea Machlitt (Bayer), Christina Mahl (Eli Lilly Deutschland GmbH) Dirk Mentzer (Paul-Ehrlich-Institut), Esther Straghan (Pfizer), Agnieszka Szmigiel (European Medicines Agency), Qun-Ying Yue (Uppsala Monitoring Centre), Lembit Rägo (CIOMS), Kateriina Rannula (CIOMS), and Pilar Rayon (Spanish Agency of Medicines and Medical Devices).

Attending virtually

Claire Brulle-Wohlhueter (Sanofi), Khedidja Hedna (International Society of Pharmacoepidemiology – ISPE / University of Gothenburg), Claudia Ianos (Pfizer), Yukiko Komori (Pharmaceuticals and Medical Devices Agency, Japan), Mahlodi Moropa (South African Health Products Regulatory Authority), Monica Munoz (United States Food and Drug Administration), Nokuthula Mayela (South African Health Products Regulatory Authority), Judith Sanabria Cabrera (Hospital Universitario Virgen de la Victoria, Málaga), Panos Tsintis (CIOMS), and Wang Yi (Center for Drug Reevaluation, China).

Apologies

Andrea Best (Gilead)