Long-term safety of medicinal products (proposal for CIOMS WG XVII)

1. Background

1.1. Why do we need long-term safety data?

Despite the large amount of preclinical and clinical safety data collected during its development, the safety profile of a new medicinal product is only partially known at the time of its approval. Indeed, the clinical trial process involves studying these medicinal products in a relatively small number of selected individuals for a short period of time. Certain side effects may only emerge once these products have been used by a more heterogenous population (specific vulnerable subgroups such as paediatrics, pregnant women, elderly) that might not be well-represented in pre-approval trials but are crucial for post marketing surveillance, including people with other concurrent diseases, and over a long period of time. That is the reason why post-marketing pharmacovigilance plays a crucial role in individuals receiving the medicinal product as it allows the identification of adverse reactions that could not be observed in clinical trials, i.e. very rare adverse reactions, adverse reactions occurring in a population with a specific risk factor, or long-term adverse reactions. It could also be adverse reactions emerging after chronic use of a medicinal product or the other extreme, a single treatment with long term effects. With advances in medicine, some patient's lives are prolonged and long-term safety issues can then arise for example (i) oncology patients in long-term remission can suffer a secondary malignancy (ii) HIV patients receiving antiretroviral treatments living long enough to be at risk of adverse cardiovascular outcomes or (iii) Patients affected with rare diseases that would have been fatal during childhood who develop long-term adverse events when they reach adulthood.

The ICH E1 guideline, initially developed in 1994, provides recommendations on the extent of population exposure needed to adequately assess the clinical safety of drugs intended for long-term treatment of non-life-threatening conditions. However, the medicinal product landscape has tremendously evolved since then and is constantly changing with the emergence of new therapies such as advanced therapy medicinal products (ATMPs), individualized cancer medicines or treatment for rare diseases.

An updated guideline is necessary to accurately reflect current and future therapeutic landscapes and provide guidance and methodology to determine whether the benefit-risk balance of a medicinal product remains favourable across lifecycle, or if the short-term established efficacy is outweighed by long-term adverse effects.

A new guideline would also significantly benefit the field by providing greater clarity, flexibility, methodological rigor, and adapted monitoring tools facilitating the timely approval and effective long-term safety monitoring of novel therapies.

1.2. The concept of long-term adverse reactions

There is no official definition of long-term adverse reactions. Generally, it refers to an adverse effect that develops after a prolonged use or a long latency adverse effect that may manifest years after being exposed to the medicinal product. However, it may also refer to an adverse effect that persists over an extended period (months or years), or an adverse effect that occurs after drug discontinuation.

While there is no formal definition, the concept around long-term adverse reactions encompasses more than traditional adverse reactions that occur during the use of the medicinal product. It captures the potential long-term biological impact of the medicinal product and associated therapeutic interventions. A few examples include:

- Biologic products, immunotherapies, and gene therapies, all of which can potentially exert delayed effects (EMA Guideline on Good Pharmacovigilance Practices, Module V, rev. 2, 2017).
- The manifestation of a "long-term" adverse reaction might be influenced by factors such as cumulative exposure, genetic predisposition, comorbidities or pre-treatment needed to allow the use of the medicinal product, such as in CAR-T therapies (CIOMS Working Group IX, 2014).

Currently, there is limited regulatory and scientific guidance tailored specifically to different therapeutic contexts (such as acute versus chronic conditions), distinct classes of medicinal products (e.g., advanced therapies, individualized cancer therapies, medicines for rare diseases), or specific safety concerns. As a result, there is insufficient clarity about the criteria or situations that necessitate long-term safety assessments. This gap makes it challenging to systematically identify when long-term safety represents an important risk, thereby highlighting the need for clear, comprehensive guidance to ensure robust patient safety monitoring and protect public health effectively.

1.3. Underlying mechanism of long-term safety concerns

This wide heterogeneity related to the fact that long-term adverse reactions may involve very different types of underlying mechanisms, such as:

- **Cumulative toxicity**: adverse effects that result from the accumulation of a drug or its metabolites in the body (or one specific organ) over an extended period.
  E.g. after months or years of daily intake, amiodarone tends to accumulate in the lungs, leading to lung damage including pulmonary fibrosis; a similar situation may occur with methotrexate and hepatic fibrosis.

- **Receptor modulation:** alteration of receptor activity related to a drug administration during an extended period for instance, long-term use of anti-psychotics may lead to upregulation of dopamine receptors due to chronic dopamine blockade, and can result in an exaggerated response to the postsynaptic receptors to dopamine, causing tardive dyskinesia.

- **Enzyme induction or inhibition**: Long-term changes in the activity of metabolic enzymes, leading to altered drug metabolism, drug interactions, and toxicity.
  One example is phenobarbital and carbamazepine, that increase the expression and activity of CYP3A4 and CYP2C9 enzymes. This leads to faster metabolism of both the inducing drug and other co-administered drugs that are substrates for these enzymes.

- **Endocrine disruption / hormonal imbalance:** endocrine disruption refers to drugs that interfere with the normal function of the endocrine system (hormone production, regulation, and signalling).
  Example: long-term use of corticosteroids can lead to adrenal insufficiency and osteoporosis by suppressing the hypothalamic-pituitary-adrenal (HPA) axis.

- **Metabolic dysregulation**: alteration of the body's metabolic processes, including the regulation of glucose, lipids, and energy balance.
  Example: Long-term use of antipsychotics can lead to metabolic syndrome, including weight gain, diabetes, and dyslipidaemia.

- **Immune system modulation**: alteration of the immune system's activity by a medicinal product, either by enhancing (immunostimulation) or suppressing its function (immunosuppression). The resulting adverse effects are variable and depend on the action of the drug on the immune system: increased risk of infections, increased risk of malignancies and risk of reactivation of latent infection for immunosuppression; chronic inflammation and autoimmune disorders for immunostimulation.
  Examples: By inhibiting key components of the immune system, biologics (Tumor Necrosis Factor (TNF) inhibitors, Interleukin (IL) inhibitors) alter the immune response. On the other hand, by enhancing the immune response against cancer, checkpoint inhibitors (e.g., nivolumab, pembrolizumab) might lead to the development of autoimmune conditions such as thyroiditis, colitis, and pneumonitis.

- **Genetic and Epigenetic changes**: genetic changes are alterations in DNA sequences (mutations). Epigenetic changes are modifications that affect gene expression without altering the underlying DNA sequence (DNA methylation, histone modification, and the action of non-coding RNAs).
  Example: Certain anticancer drugs can cause secondary malignancies due to genetic damage.

- **Dependency and withdrawal syndrome**: continuous exposure to certain drugs can result in neuroadaptive changes, leading to physical and psychological dependence characterized by withdrawal symptoms upon cessation.
  Example: Chronic use of benzodiazepines can lead to physical and psychological dependence, with withdrawal symptoms upon discontinuation.

- **O*xidative stress* and *mitochondrial dysfunction*** as underlying mechanisms of toxicity for certain therapeutic classes (e.g., some antiretrovirals, anti-epileptics) (N. Koturbash et al., *Toxicology and Applied Pharmacology*, 2011).

- **Idiosyncratic mechanisms** (such as certain immune-mediated events) may not be fully explained by traditional pharmacology (CIOMS Working Group on Drug-Induced Liver Injury, 2020).

- **Alteration of microbiome** has a potential to cause a variety of long-term safety issues. For example, the gut microbiota during early life plays a crucial role in infant development. Microbial-host interaction is also essential for metabolism, immunity, and overall human health in later life. Early-life exposure with medicines, referring to exposures such as during pregnancy, childbirth, and infancy, may change the structure and function of gut microbiota leading to later changes of human health**.**

Some long-term adverse reactions might involve several mechanisms, and many of these underlying mechanisms are interconnected. For example, a drug accumulation can be exacerbated by the

inhibition of a metabolic enzyme. Or a dependency can be related to receptor modulation for example a receptor modulation may in addition lead to hormonal imbalance.

However, in some situations, the exact underlying mechanism remains unclear. This is the case for example with bisphosphonates and osteonecrosis of the jaw, although it was identified that bisphosphonate rapidly accumulates in bone tissue and that some patients treated with bisphosphonates could experience osteonecrosis of the jaw, the exact pathogenesis is complex and remains not fully elucidated.

In summary, long-term adverse effects of medicinal products constitute a very heterogeneous category of adverse reactions, which share few common features. They rely on very different underlying mechanisms, which can also have complex interplay between them (e.g. between pharmacological and biological pathways). However, these adverse reactions can significantly impact patient safety and quality of life, making their identification and management crucial in pharmacovigilance. That is the reason why understanding long-term safety of a medicinal product is crucial from development and along the entire lifecycle.

2. Regulatory Framework

The following guidelines have applied to safety over the years and are focused primarily on safety requirements prior to medicinal product approval for marketing by regulatory authorities.

2.1. Overview of Key Regulatory Bodies and Their Guidance

- International Conference on Harmonisation (ICH) guidelines relevant to long-term safety (ICH E1 1994 Extent of Population Exposure to Assess Clinical Safety and ICH E2E on Pharmacovigilance Planning, 2004).
- European Medicines Agency (EMA) guidance on pharmacovigilance and risk management (GVP Modules, in particular Modules V, VII, and VIII).
- U.S. Food and Drug Administration (FDA) postmarketing requirements, including *FDA Guidance for Industry: Postmarketing Studies and Clinical Trials — Implementations of Section 505(o)(3) of the FD&C Act* (2011).
- MHRA guidance on pharmacovigilance in the UK (MHRA "Guidance on Pharmacovigilance Procedures," 2021).
- World Health Organization (WHO) guidance on global pharmacovigilance (WHO "Pharmacovigilance: ensuring the safe use of medicines," 2004).

The only guidance that covers exposure requirements is ICH E1 which specifies 300 to 600 patients exposed for 6 months and >100 exposed for 1 year as the minimum requirement for approval. However, it does not include any mention of criteria to be used for assessment of long-term safety and it does not take into account indication for use or medicinal lifecycle. ICH E1 applies to long term treatment in non-life-threatening conditions and applies only at the time of approval of the medicine.

Another limitation of ICH E1 is due to the assumption of large patient populations and does not adequately address the complexities inherent to rare diseases or specialized therapies (such as ATMPs and individualized treatments).

Also, the current guidelines focus predominantly on clinical trial exposure periods (one year or more), without adequate consideration for long-term follow-up beyond trial completion. Example: CAR-T cell therapies for cancers have demonstrated delayed serious adverse events (secondary malignancies, neurotoxicity), indicating the necessity of prolonged monitoring periods which significantly exceed the duration outlined by ICH E1.

ICH E1 lacks sufficient guidance on therapies that are individualized (e.g., personalized cancer vaccines, individualized cellular therapies), limiting regulatory flexibility. For example, individualized cancer vaccines, tailored specifically to patient tumour mutations, require safety assessments on a patient-by-patient basis. This precision medicine approach fundamentally challenges the generalized safety database assumptions in ICH E1.

The requirement for 1500 patient exposures is frequently impractical or impossible for rare diseases, impeding the timely development and approval of innovative treatments. Therapies for ultra-rare diseases (e.g., spinal muscular atrophy type 1, metachromatic leukodystrophy) often gain approval with limited patient numbers, relying heavily on post-marketing surveillance. The rigidity of ICH E1 is incompatible with these scenarios.

2.2. Legislative Basis for Long-Term Safety Studies

The requirements for ongoing safety evaluation once a medicine goes on the market are specified in regional legislation (e.g., Regulation (EU) No 726/2004; Directive 2001/83/EC as amended) which mandates ongoing safety evaluations for authorized products in the EU. Also, the 21st Century Cures Act (2016) in the US, which encourages the use of real-world evidence for postmarketing surveillance.

However, there is a lack of description of any criteria to be used based on product, indication, drug mode of action (MOA) or indeed safety profile that would lead to consideration of long-term safety. And yet, despite this gap in requirements the authorities do require certain medicinal products to further investigate long-term safety once they reach the market. Examples include malignancy risk in products treating non-oncology populations as well as gene therapies where a requirement of long-term follow-up (>15 years) is commonly applied and covers long-term efficacy as well as long-term safety.

2.3. Future Regulatory framework and Product Development Trends

There have been recent trends in regulations to adopt novel approaches aiming to facilitate development and access to patients in need by developing adaptive frameworks as well as integration of novel data sources (e.g. (e.g. FDA "Framework for Real-World Evidence Program," 2018).

In years to come, increasing numbers of innovative products having higher risks for long-term safety issues (increasing share of biological products including advanced therapy medicinal products (ATMP) will be developed. In pharmacovigilance the role of Artificial Intelligence (AI) to support monitoring of patient safety is gaining momentum and is already subject to international harmonization initiatives (CIOMS XIV Artificial Intelligence in Pharmacovigilance).

Given its established consensus-based approach and inclusive representation, CIOMS is uniquely positioned to develop a robust and practical framework for addressing the long-term safety of medicinal products. By actively involving diverse stakeholders - including regulatory authorities, pharmaceutical industry representatives, academic researchers, healthcare professionals, and patient organizations - CIOMS can ensure that the framework is comprehensive, balanced, and reflective of real-world complexities. This multi-stakeholder engagement fosters alignment, enhances the acceptability of recommendations across different sectors, and ensures the resulting guidance is both scientifically sound and practically implementable for safeguarding patient safety and public health in the long term.

3. Risk Management Plan: the cornerstone of long-term safety

Following ICH E2E Pharmacovigilance Planning, risk management concepts are routinely considered at the time of marketing authorisation and risk management plans (RMPs) may apply on a regional basis (RMP in EU, Japan, Canada and Australia; REMS in the US). Long-term safety can be requested to be further investigated by the company/sponsor as a risk management requirement on a regional basis. Review of established guidelines on risk management activities (GVP module V, CIOMS, ICH, etc)

3.1. Role of the Risk Management Plan (RMP) in Addressing Long-Term Risks

Long term risk can be specified by regulators in relation to the Safety Specification for a medicinal Product and may be considered an important potential risk for a medicine. In such cases, the company may conduct a post-authorisation safety study (PASS) to investigate this risk further to confirm and quantify such risk as appropriate and assess the impact, if any, on the benefit-risk of the product.

4. Medicinal products lifecycle and sources of safety data for long-term safety

As mentioned previously, the current regulatory guidelines do not apply specifically to long-term exposure and safety during the lifecycle. ICH E1 applies at the time of authorisation and does not take into account developments in knowledge regarding the medicine during later stages of its lifecycle when the long-term safety issues could emerge.

4.1. Premarketing phase:

- extended follow-up studies: despite the lack of guidance regarding long-term safety, the regulatory authorities often require long-term extension (LTE) studies for certain chronic-use products (FDA Guidance for Industry on Chronic Use Products, 2001).
- Specific populations (e.g., pediatric long-term safety follow-up after short-term oncology trials, per FDA Pediatric Research Equity Act, 2003).

4.2. Post-marketing phase

4.2.1. Spontaneous reporting

- Vital for rare or unexpected events (WHO Uppsala Monitoring Centre guidance on spontaneous reporting, 2019) but limited because of under-reporting, lack of denominator data, variable quality of reports, therefore not sufficiently reliable as a method to cover long-term safety of medicines.

4.2.2. Registries

- Disease-based or product-based registries are crucial for capturing long-term outcomes (AHRQ "Registries for Evaluating Patient Outcomes: A User's Guide," 4th ed., 2020), especially for complex medicinal products for which potential for long -term safety concerns are suspected
- Importance of linking registries with electronic health records to enhance data completeness.

4.2.3. Post-Authorisation Safety Study (PASS)

- PASS can be interventional or non-interventional and often mandated as part of regulatory obligations (EMA GVP Module VIII, rev. 2, 2017).
- Examples: Large simple safety studies, prospective cohort studies, retrospective database studies.
- Method integration: The post-marketing approaches above may be combined to address long term safety considerations as part of a risk management system for the medicinal product.

4.3. Use of Real-World Evidence for long-term safety

- Initiatives are ongoing at regional level (FDA, EMA) that focus on pharmacovigilance and which could be applicable to long-term safety as well as international developments such as CIOMS Working Group XIII on Real-World Data and Real-World Evidence in Regulatory Decision Making (CIOMS Working Group XIII report, 2024). In addition, the use of AI could be a key development as previously mentioned (CIOMS XIV). There are current challenges in these approaches including issues of data quality, confounding, and need for robust study designs (propensity-score matching, etc.).

5. CIOMS Long Term Safety Framework

It is anticipated that CIOMS Working Group XVII (WG) will develop a realistic scope based on aspects of medicinal product and potential long term safety concern. While therapeutic indication and class could be a vast scope for any detailed consideration, it is likely that the WG will develop several case study examples, including a range of these parameters. These will make the WG output as widely applicable as can be achieved within the time constraints. The WG will then aim to create a CIOMS Framework for addressing long term safety aspects in relation to medicinal products throughout their lifecycle. The CIOMs Framework will aim to provide guidance on criteria for determining the need for pharmacovigilance and risk management measures to address long term safety concerns for medicinal products.

6. Case studies to reflect on long-term safety

6.1. Lessons learned from COVID-19 pandemic and large-scale use of mRNA vaccines

- Highlight the importance of near-real-time pharmacovigilance tools (VAERS in the US, EudraVigilance in the EU) (FDA/CDC Vaccine Adverse Event Reporting System, 2021).
- Long-term follow-up for myocarditis/pericarditis, potential immune-mediated effects (EMA Pharmacovigilance updates on COVID-19 vaccines, 2022).

6.2. Long-term use in rare disease

- Example: Enzyme replacement therapies and the need for lifelong monitoring (FDA Guidance for Industry: Human Gene Therapy for Rare Diseases, 2020).
- Potential complexities of small patient populations and limited data.

7. Conclusion and future directions

Guidance on long-term safety of medicinal products is currently limited. Specific gaps include clear descriptions of relevant risk criteria, patient populations, types of medicinal products and Safety Specifications. This limitation applies particularly to regulatory requirements applied regionally that are not clear or specific and which are not presently harmonized. As this topic of long-term safety is pivotal for patients and public health, it is proposed to be addressed through the established consensus process of a CIOMS Working Group. The following are topics that could be considered within the scope of such a CIOMS WG:

1. Enhancing long-term safety monitoring

- Collaborative Data Infrastructure: The potential for global collaboration to combine registries and large databases (Innovative Health Initiative (IHI) - formerly Innovative Medicines Initiative (IMI) projects in EU). Improve reliance on collecting data from electronic health records and/or payor databases.
- Potential patient Engagement: Increased involvement of patient organizations to report and discuss long-term effects (EU Patient Registries Task Force, 2019).
- Reflect on possibility to use AI for meta-analysis and predictive analysis

- Potential to propose a **practical toolbox** helping at defining the best plan for monitoring long term-safety with decision tree and case studies as examples including how best to balance against resource use for active long-term follow-up and the likelihood of producing valuable results

2. Future directions for long-term safety

2.1. AI in PV including signal detection

- Machine learning models for disproportionality analysis of spontaneous reports (EMA Big Data Guidelines, 2021).
- Natural language processing of electronic health records and social media (FDA Sentinel Initiative, 2019).
- AI in new methodologies for real-time-real-world pharmacovigilance and risk management

2.2. Genomic Data and long-term safety

- Pharmacogenomics to predict susceptibility to serious adverse events (FDA's Table of Pharmacogenomic Biomarkers in Drug Labeling, 2023).
- Use of polygenic risk scores to tailor long-term monitoring strategies (Article: W. Green et al., *Nature Reviews Drug Discovery*, 2021).

3. Additional considerations

3.1. Methodological Approaches to Study Design

- Add a sub-section detailing robust epidemiological study designs (cohort, case-control, nested case-control, self-controlled case series) to investigate long-term risks (Rothman et al., *Modern Epidemiology*, 3rd ed., 2008).

3.2. Risk Communication

- A dedicated subsection or paragraphs on effectively communicating long-term safety risks to healthcare professionals and patients (CIOMS Working Group VIII on Practical Aspects of Signal Detection in Pharmacovigilance, 2010).

3.3. Digital Health Technologies

- Consider a brief mention of wearables, mobile apps, and telemedicine for continuous monitoring of patients in real-world settings (FDA Guidance on Mobile Medical Applications, 2015).

3. 4. Special Populations

- Expand the discussion regarding paediatric, geriatric, pregnant, and lactating populations, each of which may have unique long-term risk considerations (ICH E11(R1) for paediatric drug development, 2017; ICH E7 for geriatrics, 1993).

3.5. Multi-Stakeholder Collaboration

- Emphasize that successful long-term safety monitoring requires collaboration among product developers, regulators, academia, healthcare professionals and patients.