**CONCEPT PAPER**

**Benefit-Risk Balance for Medicinal Products – Update of CIOMS IV**

**Proposal to form a CIOMS Expert Working Group**

**Type of Consensus Action Proposed**

It is proposed that CIOMS organize a Working Group (WG) with the purpose of updating CIOMS IV on benefit-risk (B-R) balance for medicinal products throughout the medicines’ lifecycle. The WG will build on previous considerations established by CIOMS WG IV in 1998, extending the scope to include pre-approval as well as post-marketing considerations for medicinal products. The latest thinking in quantitative as well as qualitative approaches to the evaluation of benefit-risk will be incorporated, as will visual presentations of benefits and risks to improve transparency and understanding amongst key stakeholders, including patients. The perspective of healthcare professionals and patients will be considered based on other ongoing initiatives as well as new guidelines from regulatory authorities and public-private partnerships. Specific aspects of the B-R evaluation will include considerations during drug development, approval for marketing, post-marketing pharmacovigilance and risk management. The aim will be to formulate key principles to be considered during the benefit-risk evaluation at different stages of the product lifecycle. While it is recognized that ICH guidelines already exist for submissions to regulators, such guidelines do not cover real-life examples of benefit-risk assessments during different stages of the product lifecycle. The practical examples, which proved very useful in the original CIOMS IV publication, will be replaced by more recent experiences pre- and post-approval. The new WG will aim to provide practical guidance to key stakeholders - drug developers, regulators, healthcare providers and patients - on the conduct of high quality, balanced and comprehensive evaluation of benefits and risks to inform decision-making and enable access to medicines by patients who need them. This will be based on many ‘real-life’ examples from key stakeholders, using the usual collaborative consensus approach of CIOMS.

**Background**

CIOMS has developed international guidelines in many key areas of safety of medicines for decades. One of these guidelines was the CIOMS Working Group (WG) IV report on *‘Benefit-Risk Balance for Marketed Drugs: Evaluation of Safety Signals.’* To this day, CIOMS IV remains a landmark international guideline for regulatory authorities and pharmaceutical companies covering the area of post-marketing benefit-risk, a core activity for these stakeholder groups. CIOMS has subsequently elaborated concepts of methodologies for detection of drug safety signals (CIOMS WG VIII, 2010), practical approaches to risk minimisation for medicinal products (CIOMS WG IX, 2014) and evidence synthesis and meta-analysis in drug safety (CIOMS WG X, 2016). While the CIOMS WG IV benefit-risk guideline has been in use for 2 decades now and covers qualitative principles to this day, there have been further developments in our knowledge and understanding of benefit-risk concepts. These include but are not limited to initiatives taken by regulatory authorities, pharmaceutical companies and public-private partnerships as described below.

ICH has introduced guidance on B-R aspects for marketing approval submissions (M4E R2) and post-approval aggregate reporting (E2C R2). Also, the areas of pharmacovigilance (PV) and risk management have shown significant progress with proactive PV approaches emerging and a new area of risk management of pharmaceuticals gaining significant consideration. In addition, both regulators and companies have used varying approaches to conducting benefit-risk assessment of medicinal products which include traditional qualitative approaches but also, increasingly, new and emerging quantitative methods for the pre- and post-marketing phases. Knowledge and technology in this area has also advanced considerably but these advances are not yet incorporated in the day-to-day activities of regulators or industry. Furthermore, the stakeholder base has expanded: the patient is now recognized as a key stakeholder by regulators, industry, health care providers/healthcare systems, the patients themselves, patient groups and CIOMS in various processes and guidelines, including those being developed by CIOMS WG XI on patient involvement throughout the medicines’ lifecycle.

The evidence base and methodologies for safety signal detection have advanced since the original CIOMS IV publication, particularly in the post-marketing phase with enhanced data sources, use of epidemiology, meta-analysis and new statistical methods that apply to large datasets. Significant changes have also occurred in health authority regulations, developments in technologies (digital and social media), and there is increased public concern and awareness of safety issues with medicinal products. Therefore, while many of the established recommendations made by CIOMS IV are still applicable today, there are some areas including structured approaches and quantitative methods, proactive PV, signal and risk management that could be further elaborated. There is also a need to integrate all aspects of benefit-risk in a single guideline that would suit a wider stakeholder base.

Benefit-risk evaluation should start early in drug development and continue throughout the medicine’s lifecycle as long as a medicinal product is in human use. A key element in optimizing benefits and risks in clinical practice is institution of appropriate patient selection for using / not using the agent. Different targeted treatment populations and individual patients may have defined characteristics that affect the likelihood to have a therapeutic response or an adverse event. These might be determined in the drug development phase or after approval as scientific knowledge further expands, and can be used to optimize personalized patient treatment decisions.

A consistent scientific approach based on sound methodology and state of the art knowledge is therefore needed to ensure patients are treated with their medicines safely and effectively.

Key areas which merit further consideration in benefit-risk assessment include:

* Changing environment: New types of therapies (proteins, monoclonal antibodies, gene therapies); impact of population background (lifestyle, co-morbidities).
* Integration and strengthening of qualitative methods for B-R assessment pre- and post-approval.
* Consideration of new and emerging quantitative methodologies and frameworks; practical examples on the use of these pre- and post-marketing.
* Use of statistical and epidemiological methods and other outcome measures, e.g. number needed to treat (NNT) and number needed to harm (NNH).
* Regulatory initiatives: FDA and EMA B-R frameworks.
* Public-private partnerships: IMI PROTECT recommendations.
* Communication technology developments: mobile apps; internet; social media.
* The effectiveness of tools of B-R communication (e.g. label/SmPC).
* Data sources: Automated health record (HR) databases; epidemiology; electronic health records (EHR)
* Impact of risk management planning for medicinal products on B-R (extending concepts introduced in CIOMS IX);
* Milestone setting for ongoing B-R assessment;
* Need to identify specific groups within the larger targeted treatment population for whom either benefits or risks are altered;
* Need for post-market studies or enhanced pharmacovigilance to inform improvements in patient selection for treatment, as well as risk assessment and monitoring.
* Comparative benefit-risk and health technology assessment (HTA) considerations.
* Need for closer stakeholder engagement: role of patients and healthcare professionals.
* Future developments: Pharmacogenetics and individualized B-R.

All the above areas affect regional requirements for the evaluation of benefit-risk to support decision-making. However, harmonized approaches for such evaluation involving structured frameworks are currently lacking, as are guidelines for the use of novel methods and technologies.

**Issues to be considered by the WG**

* B-R evaluation, a living concept: From drug development and marketing approval to post-marketing.
* Qualitative methodologies and examples: Build on CIOMS IV qualitative aspects with new examples; build on ICH guidance on B-R with a practical focus.
* Structured framework for qualitative benefit-risk assessment.
* Quantitative methodologies and examples (IMI PROTECT).
* Optimisation of B-R: Post-market studies and enhanced pharmacovigilance
* B-R information and communication tools
* Company Core Benefit Information
* Role and involvement of stakeholders: Patients and health care providers (HCPs); drug developers, academic networks
* Individualised B-R concept
* Real life examples of benefit-risk pre- and post-marketing
* Future developments: Pharmacogenetics and individualized B-R.
* B-R Glossary

The main deliverables will be Points to Consider for B-R evaluation and a new CIOMS B-R Framework to be developed by the WG. The feasibility of developing a digital tool to facilitate use of the CIOMS B-R Framework could be considered by the Working Group.

B-R evaluation, a living concept

Benefit-risk considerations apply throughout the life-cycle of medicines from discovery to nonclinical and clinical development phases, marketing approval and subsequent use at population level. In this lifecycle, benefit as well as risk profile of a product continuously evolve, and a robust harmonised process is needed to monitor the benefit-risk balance. Methods of B-R assessment remain qualitative in nature; however, more recently various regulators and pharmaceutical companies have been involved in assessing structured and quantitative methods for B-R evaluation. The US FDA has committed as part of PDUFA VI to furthering the Agency’s implementation of structured B-R assessment into the human drug review programme: <https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm326192.htm>. In Europe, the IMI PROTECT initiative has made recommendations regarding new methodologies to be considered in B-R evaluation and EMA has used ‘effects tables’ routinely in their evaluation of new drugs for marketing authorisation. There is now a need for a more consistent harmonised approach to B-R evaluation methods to incorporate state-of-the-art knowledge. This can be supported by the development of CIOMS consensus guidelines.

ICH guidelines were revised in 2012 and 2016 to include post-marketing B-R guidelines in relation to the Periodic Benefit-Risk Evaluation Report (PBRER) and changes to the B-R section in marketing authorisation submissions, respectively:

<https://www.ema.europa.eu/documents/regulatory-procedural-guideline/international-conference-harmonisation-technical-requirements-registration-pharmaceuticals-human-use_en-0.pdf>

<https://www.ema.europa.eu/documents/scientific-guideline/ich-m4e-r2-common-technical-document-registration-pharmaceuticals-human-use-efficacy-step-5_en.pdf>

While several guidelines exist regarding B-R assessment for submissions to the regulator, covering pre- and post-approval, there is lack of a unified approach regarding criteria that determine the level or magnitude of the benefit-risk balance. There is also a lack of consensus regarding quantitative methods and their role in the B-R assessment.

Qualitative methodologies and examples

The CIOMS WG IV report remains the single authoritative publication on benefit-risk covering the post-marketing phase of medicinal product use. However, it is widely accepted that benefit-risk concepts apply from early medicines development right through to marketing approval and beyond. There is a need, therefore, to extend the CIOMS IV concept earlier in the product life-cycle. CIOMS IV was very informative in providing many practical examples of B-R evaluation and consequent decision-making. Since that time however, there have been many medicinal product safety issues, some resulting in drug withdrawal from the market and others resulting in rejection of marketing approval by regulatory authorities world-wide; it would be very timely for the CIOMS WG IV report to be updated to include these more recent real-life examples, extending the knowledge on benefit-risk assessment.

In addition, the concepts of proactive pharmacovigilance and risk management have been introduced in regional guidance and legislation and these have impacted our approach to the evaluation of benefit-risk. It is not uncommon for risk management plans to impact benefit-risk and to shift this balance favourably, thus benefiting patients. Examples include patient selection, clinical monitoring, dose modifications and many other risk mitigation strategies. The overall CIOMS IV concept, therefore, also needs to include proactive PV and risk management as a key component of current state-of-the-art B-R evaluation.

For the benefit side of the B-R equation, new aspects are becoming increasingly important such as lifestyle considerations, Quality of Life aspects, meaningful patient engagement and patient-reported outcomes (PROs). Some of these aspects are currently being developed in CIOMS WG XI on Patient Involvement in the Development and Safe Use of Medicines, and key concepts relating to benefit-risk need to be considered for their wider impact on B-R frameworks. Regarding risks, there are now new considerations regarding background co-morbidities, patient core values and lifestyle considerations at both a population and individual level that require new approaches in evaluating benefits and risks relating to medicines when used in the ‘real world’. Examples of such issues are cardiovascular or neuro-psychiatric adverse events that are being associated with drugs used in obesity.

Quantitative B-R methods and examples

The CIOMS WG IV first raised the potential for quantitative methods of benefit-risk assessment some 20 years ago. However such methods are still exploratory, there being no consensus on their role in medicines development and regulation. This is despite major progress in our knowledge and understanding of the science that underpins such methods. There is an overarching need to acquire real world outcome data on benefits and risks that are sufficiently structured and granular to inform refinements in the B-R assessment and communication steps of the B-R process. The need for new methods in this area is perhaps best shown by the very large number of methods being developed as considered by public-private initiatives such as IMI PROTECT. There is a need to further elaborate recommendations made by IMI PROTECT and to reach consensus on whether and how these methods can be integrated in our current framework for B-R assessment. CIOMS is well-placed to develop international consensus on these novel methodologies in B-R assessment. CIOMS is also an optimal forum for the elaboration of practical examples involving the use of these methods.

Benefit-risk information and communication

Regulators and industry have used well-established traditional tools to inform and communicate on benefit-risk, however it has been questioned whether these are the optimal tools to be used. While the regulatory product information tools contain large amounts of information, it can be difficult for key users such as HCPs and patients to obtain the most relevant information efficiently. There is a need to consider whether current tools are fit for purpose or whether improvements can be achieved based on current knowledge and advances in technology. This area is currently under consideration by the CIOMS WG XI on patient involvement throughout the medicines life-cycle. Any new concepts established by CIOMS XI could be incorporated within the deliberations of the updated CIOMS IV WG if they apply to benefit-risk for patients.

CIOMS has previously produced guidelines on Company Core Safety Information (CCSI) that has formed the basis for reporting safety information to regulators for decades now. This concept within a company’s core data sheet has not included the efficacy aspect, a key component of the benefit-risk balance of the medicinal product. CIOMS IV would be the appropriate forum to assess the need for core efficacy information as a means of communicating on benefit-risk with relevant stakeholders.

Real life examples of benefit-risk pre- and post-marketing

While some guidelines exist both at regional and international basis (ICH) they are focused on regulatory requirements rather than practical real-life aspects. The latter are of major importance to regulatory authority assessors, company professionals and decision makers. CIOMS is ideally placed to obtain comprehensive and recent real-life examples of benefit-risk assessment before and after approval. This aspect would be a major component of the CIOMS IV update.

**A neutral and global process is needed to develop consensus recommendations**

The task for the CIOMS group would be to develop criteria and guidelines on assessment of benefit-risk throughout the product lifecycle from drug development to marketing approval and, post-marketing, including:

* Principles of Benefit-Risk management based on current regulatory strategies and tools
* Benefit evaluation that is meaningful to stakeholders
* Integration of new approaches in signal and risk management within B-R frameworks
* Qualitative B-R: Update the CIOMS IV framework for the use of qualitative methods in assessing the benefit-risk balance of medicines both pre- and post- approval.
* Quantitative B-R: Development of criteria and a framework for the use of quantitative methods to support qualitative approaches and decision-making in Benefit-Risk.
* Points-to-consider on the Benefit-Risk evaluation of medicines that considers advances in knowledge and technology.
* Feasibility of developing a digital tool on the benefit-risk framework.
* Improved communication of benefit-risk to key stakeholders.
* Many practical ‘real-life’ examples of benefit-risk evaluation both pre- and post-approval.
* Future developments on individualized benefit-risk including pharmacogenetics.

The future WG would engage senior scientists from regulatory authorities and pharmaceutical companies, patient and healthcare professional representatives and other relevant experts in Benefit-Risk evaluation and communication. Two to three face-to-face meetings a year and email communications and TCs in-between will be organized. The composition of the WG should be balanced between stakeholders. The final delivery will be a report planned for Q4, 2022 at the latest.