The Work of the Council for International Organizations of Medical Sciences (CIOMS) in Global Pharmacovigilance

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1 Introduction

“CIOMS” is not an acronym that is widely known, and yet CIOMS guidelines have impacted and shaped the work of the World Health Organization (WHO), medicines regulatory authorities, academic organizations, the pharmaceutical industry, and other stakeholders globally in past decades. Co-founded by the WHO and UNESCO in 1949, the Council for International Organizations of Medical Sciences (CIOMS) has as its mission to advance public health through guidance on health research, including ethics, medical product development, and safety [1]. CIOMS has produced numerous guidance documents in the areas of bioethics, pharmacovigilance, and drug development and its publications have been translated into many languages including Chinese, Japanese, Russian, and Spanish [1]. This editorial provides an introduction to the work of CIOMS in the field of pharmacovigilance and highlights the relationship between the International Society of Pharmacovigilance (ISoP) and CIOMS.

2 CIOMS Organization

CIOMS is a non-governmental, not-for-profit international association under Swiss law. Since 2016, it is an observer member of the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH).

CIOMS membership is open to “organizations ... devoted to the encouragement of scientific research into the principles underlying health and into the causes of diseases, or the application of the medical sciences to the prevention and cure of diseases and to the promotion of public health” [2]. It has international members, e.g., the World Medical Association, ISoP, the International Society of Pharmacoepidemiology, and the International Union of Basic and Clinical Pharmacology as well as national members, e.g., the Academies of Medical Sciences of Belgium, Korea, and Switzerland and the Medical Research Councils of Bangladesh, India, and South Africa. In addition, there are associate members who do not meet all the membership criteria, or wish to be more like observers, e.g., the Saudi Neonatology Society. Representatives of CIOMS member organizations can be elected as Executive Committee members and can participate in the General Assembly (meets every 2 years and alternate years by teleconference, decisions are adopted by consensus), [2] and the member organizations are kept informed of CIOMS, ICH, and WHO activities and publications.

The CIOMS member organizations, through their own members, for example the World Medical Association’s national associations of physicians, represent a substantial part of the global biomedical scientific community [1]. In contrast, CIOMS itself is an extremely lean organization with just four staff working at its Secretariat in Geneva. A commissioned survey among CIOMS members, which was presented at the 2019 General Assembly, found that CIOMS lacked public relations capacity to promote itself, resulting in a relatively low general visibility, but was nevertheless perceived by those involved in CIOMS work as being “at the apex of big players in global health/science” and as a respected scientific neutral platform that provides a voice to all, including people in resource-limited settings (Mark Kays, personal communication, 18 December 2019).

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3 CIOMS Activities

The Council's current work model relies on establishing technical Working Groups (WGs) to develop guidance on topics where knowledge and practice gaps need to be covered worldwide. The groups consist of international experts from regulatory authorities, the pharmaceutical industry, academia, and research organizations. The composition and discussions of the WGs are made transparent in the meeting minutes published on the CIOMS website. It usually takes 2–4 years for a WG to publish its recommendations in the form of a final report. An exception has been the group working on Standardized MedDRA® Queries, which was active from 2002 to 2019 and developed over 100 Standardized MedDRA® Queries during that time. This work was carried out in collaboration with the ICH MedDRA Management Committee and with the participation of the MedDRA® Maintenance and Support Services Organization. Today, the maintenance and creation of new Standardized MedDRA® Queries are the responsibilities of the Maintenance and Support Services Organization.

While the CIOMS WG recommendations are not per se legally binding, many of their principles have been implemented in ICH guidelines (see below) as well as national and regional regulations. They also serve as informational and educational resources. For example, the CIOMS ethical guidelines [3], which were prepared in collaboration with the WHO, are designed to facilitate the practical implementation of the Declaration of Helsinki in all parts of the world and have been used as a centerpiece of teaching in ethical training programs [4].

One of the prime functions of CIOMS has traditionally been to act as a “sounding board” for new ideas and directions in the evolving fields of pharmacovigilance, bioethics, and drug development [5]. The unique value of CIOMS as a consensus-building platform has been described thus by a member of five of the early CIOMS pharmacovigilance WGs: “The benefit of the CIOMS forum was as a neutral, comprehensive “think tank” in which stakeholders could develop trust in each other and discover their common ground. With that trust and common ground recognition, we were able to develop documents that expressed strategic goals, specific process ideas and consensus aspirations” [6].

3.1 CIOMS Pharmacovigilance WGs

Pharmacovigilance has been one of the core activities of CIOMS WGs for almost four decades. In the early 1980s, in close collaboration with the WHO, CIOMS launched

its program on Drug Development and Use—Medical, Social and Economic Implications. The stimulus for this joint program was a conference held in 1997 [7], where it was recognized that CIOMS, as an independent organization, was well placed to bring policy makers of research-based pharmaceutical industries into discussion with their counterparts in government and academia, and to convene groups of experts from these constituencies [8].

The first CIOMS Pharmacovigilance WG started when representatives from the pharmaceutical industry approached CIOMS, asking for help in negotiating a harmonized approach with leading regulators because of the emergence of regulatory requirements for the individual case safety report reporting from several countries, all requesting different formats (Sten Olsson, personal communication, 2 June 2020). The group recommended that representatives of industry and governments should convene to consider methods of standardizing government reporting requirements [5]. This resulted in the CIOMS-I reporting form, which is now adopted globally. However, not all countries wanted to receive individual case safety reports from the marketing authorization holders, but wanted companies to take responsibility for assessment of case report data and produce summary reports. This request led to the WG II being convened, and subsequently recommending the precursor of the periodic safety update report. Subsequent WGs targeted additional emerging aspects of pharmacovigilance (Table 1).

When ICH was founded in 1990 to develop harmonized regulatory guidelines on the quality, safety, and efficacy aspects of pharmaceutical products, along with multidisciplinary guidelines, the CIOMS consensus reports had created precedents for the standardization of adverse reaction reporting and monitoring for marketed drugs [9]. Consequently, the CIOMS recommendations were taken up in several ICH Efficacy Guidelines, forming the basis of modern pharmacovigilance (Table 1).

Today, some of the principles recommended by CIOMS WGs form an integral part of daily practice of both regulatory authorities and the pharmaceutical industry. For instance, the categorization of adverse effects by their frequency on an exponential scale, from “very common” (occurring in one or more of every ten patients treated) to “very rare” (occurring in less than one of every 10,000 patients treated) [10], was taken up in the European Medicines Agency's guideline on the Summary of Product Characteristics [11] and is used today in patient information leaflets throughout Europe. Another example is the Roussel Uclaf Causality Assessment Method, also known as the CIOMS scale, which was the outcome of an international consensus meeting in 1989 led by CIOMS [12]. This algorithm remains one of the most widely used tools for the diagnosis of drug-induced liver injury and herb-induced liver

Table 1 Council for International Organizations of Medical Sciences (CIOMS) Pharmacovigilance Working Group (WG) reports, and their adoption in International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines
Source: Adapted from CIOMS Special Newsletter 11 April 2019 [6]

WG	Report title	Publication year	Uptake in ICH guidelines
CIOMS WG I	Monitoring and Assessment of Adverse Drug Effects	1986	E2A
CIOMS WG I (separate ADR W)	International Reporting of Adverse Drug Reactions	1987	
CIOMS WG II	International Reporting of Periodic Drug Safety Update Summaries	1992	E2A, E2B, E2C
CIOMS WG III	Guidelines for Preparing Core Clinical Safety Information on Drugs	1995	E2C
CIOMS WG IV	Benefit-Risk Balance for Marketed Drugs	1998	
CIOMS WG V	Current Challenges in Pharmacovigilance: Pragmatic Approaches	1999	E2D
Series of international WGs convened by CIOMS	Reporting Adverse Drug Reactions: Definitions of Terms and Criteria for Their Use	1999	
CIOMS WGs III and V	Guidelines for Preparing Core Clinical Safety Information on Drugs (Second Edition)	1999	E2F
CIOMS WGs on SMQs and SMQ Implementation ^a	Development and Rational Use of Standardized MedDRA Queries (SMQs): Retrieving Adverse Drug Reactions with MedDRA	2004	Developed by WG, SMQs are ICH products
CIOMS WG VI	Management of Safety Information from Clinical Trials	2005	
CIOMS WG VII	Development Safety Update Reports (DSUR): Harmonizing the Format and Content for Periodic Safety Report During Clinical Trials	2006	
CIOMS WG VIII	Practical Aspects of Signal Detection in Pharmacovigilance	2010	
CIOMS/WHO WG	Definition and Application of Terms for Vaccine Pharmacovigilance	2012	
CIOMS WG IX	Practical Approaches to Risk Minimisation for Medicinal Products	2014	
CIOMS SMQ Implementation WG ^a	Development and Rational Use of Standardised MedDRA Queries (SMQs): Retrieving Adverse Drug Reactions with MedDRA (Second Edition)	2016	Developed by WG SMQs are ICH products
CIOMS WG X	Evidence Synthesis and Meta-Analysis for Drug Safety	2016	
CIOMS WG on Vaccine Safety	CIOMS Guide to Active Vaccine Safety Surveillance	2017	
Subgroup 3 of the CIOMS WG on Vaccine Safety	CIOMS Guide to Vaccine Safety Communication	2018	
CIOMS WG on Drug-Induced Liver Injury	Drug-Induced Liver Injury (DILI): Current Status and Future Directions for Drug Development and the Post-Market Setting. A Consensus by a CIOMS Working Group	2020	

ADRs adverse drug reactions, SMQs standardized MedDRA[®] queries, WHO World Health Organization

E2A: ICH E2A (1994): clinical safety data management—definitions and standards for expedited reporting

E2B: ICH E2B (2001, revision released for consultation 2005; finalized 2012): clinical safety data management—data elements for transmission of individual case safety reports. A table of fields in the CIOMS I form and the corresponding data elements in ICH E2B are found underneath the CIOMS I form posted on the CIOMS website [1]

E2C: ICH E2C (1996): clinical safety data management—Periodic Benefit-Risk Evaluation Reports (PBRER)

E2D: ICH E2D (2003): post-approval safety management—definitions and standards for expedited reporting

E2F: ICH E2F (2010): development safety update reports

ICH efficacy guidelines are available at: <https://ich.org/page/efficacy-guidelines>

^aThis WG was based on the Memorandum of Understanding with the ICH MedDRA Management Board

Table 2 Active Council for International Organizations of Medical Sciences (CIOMS) Working Groups (WGs) Source: CIOMS website, <https://cioms.ch>

WG	Year established
CIOMS WG on clinical research in resource-limited settings	2017
CIOMS WG XI on patient involvement in the development and safe use of medicines	2018
CIOMS WG on MedDRA labeling groupings (MLGs)	2019
CIOMS WG XII on benefit-risk balance (update of CIOMS IV report on benefit-risk balance for marketed drugs: evaluation of safety signals)	2019
CIOMS WG XIII on real world evidence and real world data in regulatory decision-making	2020

injury [13]. A discussion of the use and limitations of the Roussel Uclaf Causality Assessment Method is included in the recently published consensus report of the CIOMS WG on Drug-Induced Liver Injury [14].

3.2 Current CIOMS WGs

The emerging CIOMS WGs are gaining attention exponentially and the resultant work is expected to be a valuable source of guidance on the safe and effective use of medicines. There are currently five active CIOMS WGs (Table 2). A new group on severe cutaneous adverse reactions is planned to commence work in the third quarter of 2020 (Le Louet Hervé, personal communication, 25 August 2020).

4 ISoP and CIOMS Relationship

Both ISoP and CIOMS share a common goal of advancing pharmacovigilance at all levels, and it is fitting that a past ISoP president, Prof. Hervé Le Louet, is the president of CIOMS. ISoP members have been instrumental in identifying new topics for CIOMS WGs, for example, Prof. Le Louet proposed and led the Drug-Induced Liver Injury WG, and individual ISoP members have participated in many CIOMS WGs. The most recent example is the CIOMS WG XI on Patient Involvement in the Development and Safe Use of Medicines, where ISoP has been represented by Sten Olsson, Brian Edwards, and Manal Younus. All three have actively contributed to the draft text, particularly to the chapter titled “Guiding principles for patient participation in the generation and utilization of safety and effectiveness data” [15]. The WG XI will provide recommendations on why, how, and when to engage patients at all stages of the development and safe use of medicines. The work is now at an advanced stage. The final report will be the guidance document in this area to be developed jointly by representatives from academia, the pharmaceutical industry, patient organizations, the World Medical Association, and regulatory authorities, and the first to look at the global landscape of patient involvement, including the challenges and opportunities in

resource-limited settings. The added value of the collaboration between ISoP and CIOMS is expected to shape the future relationship of the two organizations, anticipating that they will work together even more closely with more structured engagement of each other’s activities.

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