Council for International Organizations of Medical Sciences

First meeting of the CIOMS Working Group on Drug-Induced Liver Injury (DILI)

27-28 April 2017, Geneva, Switzerland

Minutes (web)

CIOMS background

(adapted from CIOMS homepage: http://www.cioms.ch):

"The Council for International Organizations of Medical Sciences (CIOMS) is an international, non-governmental, non-profit organization established jointly by WHO and UNESCO in 1949.

In 2013, the membership of CIOMS included 49 international, national and associate member organizations, representing many of the biomedical disciplines, national academies of sciences and medical research councils. The main objectives of CIOMS are:

- To facilitate and promote international activities in the field of biomedical sciences, especially when the participation of several international associations and national institutions is deemed necessary;
- To maintain collaborative relations with the United Nations and its specialized agencies, in particular with WHO and UNESCO; and
- To serve the scientific interests of the international biomedical community in general.

To achieve its objectives, CIOMS has initiated and coordinates the following main long-term programmes:

- Bioethics
- Health Policy, Ethics and Human Values - An International Dialogue
- Drug Development and Use
- International Nomenclature of Diseases"

CIOMS working groups are typically planned for three years, focusing on a specific topic. Operating model includes two face-to-face meetings per year, and regular subgroup meetings in between. CIOMS secretariat provides logistical support and helps coordinating activities.

Scope of the CIOMS working group on DILI is to establish a global perspective on liver signal detection, assessment, and risk management in drug development and post-marketing.

Meeting objectives

- Identify key challenges to focus on
- Develop WG business plan
- Set up subgroups to address key topics
- Identify other key DILI initiatives to interact with*

**Post-meeting note: mapping the CIOMS WG to other DILI initiatives in order to avoid overlap and duplications may still have to be discussed in more depth and assigned to one of the subgroups; possibly group 3?*

Introductory session

Short introductory presentations were given on CIOMS, as well as academic, industry, and regulatory perspectives regarding DILI. The following key discussion points emerged:

- What are adequate criteria for DILI case definition, characterization and classification of phenotypic subgroups in DILI?
- Are herbal and dietary supplements within or out of scope?
- Gaps and challenges with data collection and causality assessment pre and post marketing
- Best practices for data ascertainment, management, and analysis
- Utilization of new liver safety biomarkers
- Proper communication of DILI risk to patients and prescribers
- Adequate risk management and risk minimization

Accordingly, three subgroups were formed, each with contribution from industry, academia, and regulatory agencies:

1. **Group 1: Principles in Detection, Characterization and Risk Assessment of DILI in Clinical Trials and Post Marketing**
2. **Group 2: Liver Safety Biomarkers: Recommended strategies for pre-marketing and post-marketing studies and efforts**
3. **Group 3: DILI risk stratification, minimization, and communication**

Breakout sessions

Group 1

Focus areas:

- Definition of DILI phenotypes
  - Clinical
    - Hepatocellular
    - Cholestatic
    - Mixed
    - Chronic steatosis/ steatohepatitis
    - Acute on chronic liver failure
    - Chronic liver injury post-hepatocellular DILI
    - Others

	○ Related to specific therapies	▪ Immunotherapy ▪ Other biologics
• Data Ascertainment	○ Minimal required data ○ Clinical narrative ○ Biological samples ○ Liver biopsy	
• Data Collection Forms		
• Data Analysis in Clinical Trials	○ Interpretation of liver injury signals ○ Cases of interest ○ Imbalance of ALT and AST elevation (for hepatocellular) ○ Imbalance of ALT & TBL elevation ○ Hy's Law cases ○ Visual/graphical tools	▪ eDISH ▪ Others
• Data Analysis Post Marketing	○ Importance of reporting ○ Report quality ○ Who is reporting? ○ Clinical narratives ○ Databases	▪ Drug companies ▪ Clinicians ▪ Others ▪ Clinical history ▪ Differential Diagnosis ▪ FAER ▪ EUDRA Vigilance ▪ PMDA Database
• Causality Assessment	○ Methods	▪ RUCAM ▪ Expert opinion ▪ Others

Group 2

Focus areas:

• Limitations of standard markers		
• Definition of biomarker categories	○ Quality	▪ Known valid ▪ Probable valid ▪ Exploratory

	○ Type	▪ Diagnostic ▪ Prognostic ▪ Predictive
• Associated (patho)physiological processes	○ Hepatocellular injury ○ Cholestatic injury ○ Mitochondrial injury ○ Hepatocellular regeneration ○ Immune activation ○ Functional capacity ○ Mechanistic (apoptosis vs necrosis) ○ Drug-protein adduct formation	
• Considerations for biomarker qualification		
• Adequate interpretation of biomarker results		
• Relevant sample material	○ Whole blood ○ Serum ○ Lymphocytes ○ DNA ○ Urine ○ Stool ○ Liver tissue	
• Relevant time points by matrix	○ Screening ○ Baseline ○ On treatment ○ End of treatment ○ Follow-up: post-treatment observation time dependent on biomarker half-life	
• Ethical issues, content and language of ICF for biomarker sampling and assessment		
• Sampling and storage processes for biomarker collection		
• Collection in control groups, definition of healthy controls		
• Storage time	○ 5 -10 years post regulatory approval?	
• Challenges for sample collection post marketing	○ Lack of baseline ○ Heterogeneous presentation at time of diagnosis ○ Sampling without incentive	

Group 3

Focus areas:

• Quantitative and qualitative risk	
• Risk severity according to phenotype	
• Risk factors	○ Age ○ Gender ○ Time to onset ○ Co-medications ○ Interactions ○ Administration route
• Differentiation by indication	○ Oncology ○ Cardiovascular
• Current labelling in each country/region	
• Risk mitigation measures	

Final discussion

It was envisaged that the next face-to-face meeting should be around October. By then, an early draft of the report should be available. Subgroup chairs will lead the compilation of the draft.

The core document should focus on robust recommendations. Perspectives more bound to change over time should go in appendices.

Recommendations in the report will not have binding character, but will reflect consensus opinion of the CIOMS DILI group.

The audience of the paper will be across public stakeholders, regulatory bodies, investigators, and practitioners.

A project platform, e.g. SharePoint, Dropbox etc. is desirable. The CIOMS Secretariat may be able to help with that.

Place and date of next meeting

Post-meeting note: The meeting was scheduled to take place in Málaga, Spain, on 14–15 November 2017.

Participants

CIOMS	Hervé **Le Louet**	APHP, CIOMS President
	Lembit **Rägo**	CIOMS Secretary-General
WHO	Daisuke **Tanaka**	Safety and Vigilance Team (SAV)
Regulators	Mark **Avigan**	U.S. FDA
	Uzu **Shinobu**	PMDA Japan
	Haibo **Song**	CFDA China
	James **Southern**	SAHPRA / Medicines Control Council South Africa
	Hajime **Takikawa**	Teikyo University, consultant of MHLW, Japan
	Mari **Thörn**	MPA Sweden
	Jean-Marc **Vidal**	European Medicines Agency (EMA)
Academia	Raul **Andrade**	University of Málaga, Spain
	Einar **Björnsson**	National University of Iceland
	Robert **Fontana**	University of Michigan, U.S.
	Maribel **Lucena**	International Union of Basic and Clinical Pharmacology (IUPHAR)
Industry	Amel **Benkritly**	Sanofi
	Michele **Bortolini**	Hoffmann La Roche
	Michael **Merz**	Novartis (stepping in for Gerd Kullak-Ublick)
	Arie **Regev**	Eli Lilly
	Javier **Waksman**	Pfizer
	Hui-Talia **Zhang**	Bayer

Apologies

Regulators	Marc **Blockman**	SAHPRA / Medicines Control Council South Africa
	Patricia **Mandali de Figueredo**	ANVISA Brazil
	Anil **Nayyar**	FDA
	Elmer **Schabel**	EMA
	Thorsten **Vetter**	EMA
WHO	Shanthi **Pal**	Safety and Vigilance Team (SAV)
Consortia	John-Michael **Sauer**	C-Path Predictive Safety Testing Consortium
Industry	Gerd **Kullak-Ublick**	Novartis
	Geoffrey **Ross**	Takeda
	Walter **Straus**	Merck

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