Council for International Organizations of Medical Sciences

Fourth meeting of CIOMS Working Group (WG) on Drug-Induced Liver Injury (DILI): 27-28 November 2018, Aix-en-Provence, France

Minutes (web)

Opening

Lembit Rägo opened the meeting and conveyed apologies from Hervé Le Louët, who had to attend to a safety issue related to medical devices. Dr Agnès Lillo-Le Louët welcomed the participants to her native Aix-en-Provence. She outlined the history of the town and of the meeting venue, Hôtel de Gantès, which was frequented by the painter Paul Cézanne, the writer Emily Zola and other prominent figures of their time.

The following new participants introduced themselves: Jia-Bo Wang (Institute of Chinese Herbal Medicine, Beijing 302 Hospital), Yimin Mao (RenJi Hospital, Shanghai, JiaoTong University School of Medicine), Xing Min Qiu (Pfizer), Alexandre Kiazand (AstraZeneca), and Monika Zweygarth (technical writer, CIOMS Secretariat). Monika will facilitate the consolidation of texts drafted by each group and do the final editing of the overall report.

A list of meeting participants is shown in **Annex 1**.

Minutes: Maribel Lucena assisted by Monika Zweygarth and James Southern, with input from Guruprasad Aithal and subgroup chairs.

Agenda, approval of previous meeting minutes

The agenda and previous meeting minutes were provided to the participants.

The minutes of the 3rd Working Group meeting, held in Reykjavík, Iceland, on 8-9 May 2018 were adopted. Lembit Rägo reminded participants that minutes of CIOMS WG meetings are now being made available on the CIOMS website to enhance the transparency and visibility of the Working Groups' activities.

Updates on other DILI initiatives

FDA-AASLD DILI meeting

Mark Avigan encouraged the participants to attend the next annual meeting co-hosted by the U.S. Food and Drug Administration (FDA) and the American Association for the Study of Liver Diseases (AASLD), to be held in Washington on 7-8 May 2019[1]. A broad range of relevant topics will be discussed. A poster session on recent data on DILI -related topics has been accepted. It was suggested to summarize the main ongoing initiatives on DILI in oral presentations, if possible.

COST Action 17_112 Pro EURO DILI Network

Raul J Andrade presented an update from the Prospective European Drug-Induced Liver Injury Network (Pro-Euro DILI Network), which he is chairing with Guruprasad Aithal as Vice-Chair. This multidisciplinary network of experts is part of the European Cooperation in Science and Technology (COST). Its aims are to pre-empt and prevent DILI, to improve clinical care and outcomes, and to foster translational research, public awareness and education. Current working group topics are: phenotyping in DILI, risk stratification, preclinical evaluation, clinical trial and investigation design, and dissemination/communication. The 1st Management Committee meeting was held in Brussels on 16 October 2018. The Network is open to interested members from any country. Current membership is from 21 European countries, China, India, the United States, Uruguay and Chile. The website is currently under construction.

In the discussion it was clarified that the main aims of this platform are networking, promoting best practices, and education. It is not geared towards research.

IQ-DILI initiative

Arie Regev presented an update from the IQ-DILI Initiative established in 2016 under the International Consortium for Innovation and Quality in Pharmaceutical Development (IQ)[2]. IQ-DILI currently includes 15 IQ member companies and over 60 industry participants, and has engaged with representatives from over 20 different organizations and academic institutions in the past year (TransCelerate, The Liver Forum, U.S. National Institute of Health NIH, and others). There are six working groups focusing on the following topics: (1) abnormal baselines, (2) causality assessment, (3) immunotherapy, (4) biomarkers, (5) translation of non-clinical toxicology findings into clinical trial monitoring and assessment, and (6) post-marketing pharmacovigilance. Additional topics have been identified, such as: paediatric population, elderly patients, biologicals other than checkpoints inhibitors, and drug rechallenge. IQ-DILI is preparing for its Phase II, in which it will engage in cross-company clinical data-sharing to advance best practices for DILI prevention, detection, monitoring, and management.

IMI2 TransBioLine project

Guruprasad Aithal presented a status update from the Translational Safety Biomarker Pipeline (TransBioLine) project on behalf of Michael Merz. This will be funded by the European Commission's Innovative Medicines Initiative 2 Joint Undertaking (IMI2) and will focus on development of biomarkers, including liquid biopsies, of injury of the liver and other organ systems in clinical trials and post-marketing[3]. The proposal has passed the Stage 2 IMI hearing successfully in September. The project is expected to be launched in February 2019, after signature of the grant agreement and the consortium agreement.

[1] https://www.fda.gov/Drugs/NewsEvents/ucm624334.htm
[2] https://www.iqdili.org/
[3] https://www.imi.europa.eu/sites/default/files/uploads/documents/apply-for-funding/call-documents/imi1/DraftTopic2017_Transbioline.pdf

Progress reports from the subgroups

The Group Chairs presented progress updates on drafting of the report sections allocated to each group. The general and technical topics discussed during these sessions are summarized below.

Some areas of overlap between the drafts of the groups were also discussed. This discussion was continued on Day 2 of the meeting. The outcomes are reflected under "Report-back from group sessions" (pp. 4 ff.) and in **Annex 2**.

Group 1: Principles in Detection, Characterization and Risk Assessment of DILI in Clinical Trials and Post Marketing

Arie Regev presented an update from Group 1. The sections are at an advanced stage of drafting; some of them need to be shortened.

Overlaps were identified between the section on DILI in Japan covered by Group 1 and the overview of registries covered by Group 2 (see Annex 2). These two sections will be reconciled to avoid any contradictions and minimize duplication.

Scope of recommendations: It was suggested that the CIOMS report should provide high level recommendations that can be taken up around the world.

Samples: Data analysis on DILI depends on collection of samples using a consistent methodology, appropriate storage and documentation. CIOMS could recommend storage of "for-safety" samples for future testing as and when required. It was noted that not all companies find this cost-effective.

CIOMS DILI Case Report Form: Group 1 is drafting a model Case Report Form ("e-CRF") specific to DILI. This will have a checklist of data to collect in case of suspected DILI, and will be triggered by a threshold biomarker value defined in companies' clinical trial protocols. The threshold can be flexible and can be altered depending on the trial. The form will have an algorithm listing the questions that clinicians/investigators need to answer, so that information is collected systematically and consistently to make sense for a reviewer.

In the discussion it was suggested that the form and underlying advice should be kept simple, easy to follow for investigators and study co-ordinators, and relevant to ensure that the information helps decision-making and adjudication. Participants discussed some specific considerations in this regard, e.g.: use of coded fields linked to defined terminologies, importance of dates of onset and duration, and inclusion of a narrative field for remarks. Based on the information entered by clinicians, adjudication would be done in three steps: (1) Ascertaining point data, (2) considering narrative information, and (3) the actual causality assessment. The first two steps will be described in the white paper being drafted by Group 1; the third step is separate from the proposed DILI "e-CRF".

Participants also discussed how the proposed CIOMS DILI "e-CRF" would be linked with the e-CRF related to each specific trial, and to what extent it adds value or increases the burden of data collection. It was suggested to make the case that the **cost of not collecting data** (and therefore not being able to adjudicate DILI cases correctly) may be higher than the cost to companies of implementing the CIOMS DILI form.

The consensus was that the information and the CIOMS form would be helpful. It was also agreed that the form should be offered electronically. It will be made available on CIOMS website for adaptation by companies, and will be updated periodically in light of user feedback and scientific advances. CIOMS would be willing to find ways to maintain this form, if the Working Group decided that it is a good idea and that the form should be proposed as a standard.

Group 2: Liver Safety Biomarkers: Recommended strategies for pre-marketing and post-marketing studies and efforts

Most texts are at an advanced stage. Some sections need to be shortened; a few are still at the outline stage.

(Post-meeting note: an amended version for editing was shared by Bob on 1 December).

CIOMS report format: During this update the participants commented as follows on the format of the WG report as a whole.

- **Section summaries:** Each of Group 2's main section opens with a summary of issues and recommendations. This should be done across the document to improve readability. The main headings and the summaries will provide a concise overview of the CIOMS guidance.
- **Updateable supplementary materials:** The draft document includes some comprehensive information – e.g. on registries and epidemiological studies – that is rapidly evolving. Such information will be introduced briefly in the main text, with full updateable info in an electronic appendix. CIOMS will find ways to ensure that this supplementary information stays current.

Group 3. DILI risk stratification, risk minimization measures and risk communication

This group has drafted approximately 90 pages in total; the document needs editing and formatting. In reviewing this group's progress the following related topics were discussed:

Labelling: Current product labeling on DILI is inconsistent for several reasons: data on DILI themselves are scarce and inconsistent, regulatory requirements differ between jurisdictions, the labels are negotiated case-by-case with regulators at the time of approval, and they are not systematically updated thereafter. The importance of labelling in mitigating DILI risks was discussed. CIOMS can make an aspirational recommendation calling for harmonization of labels with a clear risk characterization.

Monitoring: This is complex, specific to each product and patient, and hampered by a lack of data. Nevertheless some basic CIOMS recommendations on monitoring would be valuable. Specifically, it would be helpful to include guidance on the relationship of ALT vs AST as indicator of DILI (with links to the Biomarker section as appropriate).

Group breakout sessions

On Day 1 p.m. and Day 2 a.m. the three groups discussed separately how to proceed with completing their drafts.

Report-back from group sessions

Outline and overlaps: Each group outlined the content of their sections. Some overlaps were identified and decisions made on how to address them (see **Annex 2**). It was noted that overlaps are inevitable and can be useful, as long as there are no contradictions and minimal redundancies.

Other CIOMS reports: Useful material, e.g. definitions and a description of sources of data on adverse effects, may be found in prior CIOMS reports. Relevant reports will be shared with the WG.

(Post-meeting note: The following reports have been uploaded to the WG member area on the CIOMS website:

- *Management of Safety Information from Clinical Trials: Report of CIOMS Working Group VI*
- *Development Safety Update Report (DSUR) Harmonizing the Format and Content for Periodic Safety Report during Clinical Trials: Report of CIOMS Working Group VII* ***(copyright document – not for distribution)***

- *Practical Aspects of Signal Detection in Pharmacovigilance: Report of CIOMS Working Group VIII* ***(copyright document – not for distribution)***
- *Practical Approaches to Risk Minimisation for Medicinal Products: Report of CIOMS Working Group IX* ***(copyright document – not for distribution)***

Way forward

Consolidated drafts for editing: At the 2nd WG meeting in Málaga it had been decided to form an editorial team composed of the CIOMS Secretary-General, WG and subgroup chairs, Mark Avigan as regulatory representative, Walter Straus as industry representative, and both rapporteurs. At the 4th Meeting it was agreed that the Group Chairs should consolidate the current draft(s) in a single document and share it with the full WG for comment. Monika will then combine the three texts and edit the document to make it user-friendly for a global readership.

Timelines: The aim is to publish the DILI guidance in 2019. Given the availability of editorial support at CIOMS it would be best if editing could start as soon as possible.

Date of next meeting

The 5th DILI Working Group Meeting will be held in Tallinn, Estonia, on 15-16 May 2019.

Annex 1: Participants

* = new participant

CIOMS	Hervé **Le Louët**	APHP, CIOMS President (part of Day 1 only)
	Lembit **Rägo**	Secretary-General
	*Monika **Zweygarth**	Technical writer
Academia / Clinicians	Guruprasad **Aithal**	University of Nottingham, United Kingdom
	Raul J **Andrade**	University of Málaga, Spain
	Einar **Björnsson**	National University of Iceland
	Robert **Fontana**	University of Michigan
	Maribel **Lucena**	International Union of Basic and Clinical Pharmacology (IUPHAR)
	*Yimin **Mao**	RenJi Hospital, Shanghai JiaoTong University School of Medicine, China
Regulators	Mark **Avigan**	U.S. FDA
	Uzu **Shinobu**	Pharmaceuticals and Medical Devices Agency (PMDA), Japan
	Monica **Soares**	ANVISA, Brazil
	James **Southern**	South African Health Products Regulatory Authority (SAHPRA)
	Hajime **Takikawa**	Teikyo University, Consultant of Ministry of Health, Labour and Welfare (MHLW), Japan
	Mari **Thörn**	Medical Products Agency (MPA), Sweden
	Jean-Marc **Vidal**	Formerly: European Medicines Agency (EMA)
	*Jia-bo **Wang**	Beijing 302 Hospital of China
Industry	Michele **Bortolini**	Roche
	Stewart **Geary**	Eisai (Day 2 only)
	*Alexandre **Kiazand**	Astra Zeneca
	Gerd **Kullak-Ublick**	Novartis
	John **Marcinak**	Takeda
	Manfred **Oster**	Sanofi
	*Xing Min **Qiu**	Pfizer
	Arie **Regev**	Eli Lilly
	Walter **Straus**	Merck
	Javier **Waksman**	FibroGen
	Hui-Talia **Zhang**	Bayer

Apologies

World Health Organization (WHO)	Shanthi **Pal**	WHO Safety and Vigilance Team (SAV)
Regulators	Mark **Blockman**	South African Health Products Regulatory Authority (SAHPRA) – represented by James Southern
	Elmar **Schabel**	European Medicines Agency (EMA) – represented by Jean-Marc Vidal
	Haibo **Song**	CFDA, China
Academia / Clinicians	Michael **Merz**	University Hospital Zurich, Switzerland
Consortia	John-Michael **Sauer**	C-Path Predictive Safety Testing Consortium
Industry	Geoffrey **Ross**	Takeda – represented by John Marcinak

Annex 2: Overview of report sections

Group / Section	Remarks
Group 1: Principles in Detection, Characterization and Risk Assessment of DILI in Clinical Trials and Post Marketing	
Introduction Liver biopsy for DILI Assessment Case Report Forms for DILI	A single introduction for the entire guidance document **Liver biopsy**: to be covered by Group 1
Definitions of Clinical Phenotypes Liver injury related to immunotherapy for cancer Minimal required data Causality Assessment	**Phenotypes**: Introduction of concept. (Additional detail covered by Group 3) Immunotherapy: To be matched with **Immunotherapy:** Match with Group 3's draft **Rechallenge** for diagnostic purposes to be covered here
Principles of Preclinical Assessment of DILI	
Data Analysis in Clinical Trials	**Severity assessment:** to be covered by Group 1
DILI in Japan	To be reconciled with Group 2's section on biomarkers and post-market registries, including from Japan
Safety Surveillance and Post-Marketing Data Analysis of DILI	**Pharmacovigilance:** Overview; DILI-specific (and selected aspects covered by Groups 2 and 3)
DILI Case Narratives	Case narratives could go into an appendix
Group 2: Liver Safety Biomarkers: Recommended strategies for pre-marketing and post-marketing studies and efforts	
Biomarker definitions and contexts of use	
Biomarker performance characteristics	
Current standard liver safety biomarkers: applications, interpretation, adaption versus progression, monitoring liver toxicity in clinical trials, severity	**DILI Severity:** keep section brief, concept covered by Group 1
New biomarkers (requirements, current exploratory biomarkers, recommendation on application and exploration)	
Ethical issues and considerations	
Postmarketing pharmacovigilance	**Pharmacovigilance:** Overview of data streams, role of registries
Challenges with liver signal detection and assessment	Need a diagram of overall streams of data (check previous CIOMS reports, adapt and reference as appropriate)
Current efforts by regulatory agencies in US, Europe and Asia	
Current efforts by European, US, and other DILI Networks	**Registries:** Short version in main text, full updateable info in an appendix
Epidemiological studies based on large DILI cohorts	
Group 3: DILI risk stratification, risk minimization measures and risk communication	
Introduction; gaps and challenges: Principles of risk stratification for DILI, possibility of using large scale electronic medical database to identify DILI reports	
"What kind of risk"and harms of DILI phenotypes Characterize drug and host risk factors of DILI	**Phenotypes,** **Severity scaling:**
Severity categorization in product labeling and communication. Challenges of using the Common Terminology Defining severity (of DILI) is a good objective. CT-AE Guidance	Introduced briefly upfront, details here in specific context Agreed on Unlikely – possible – probable and above. Undetermined when not sufficient information

Continued on next page

Group / Section	Remarks
Continued from previous page – Group 3: Effective risk management Effectiveness of DILI risk characterization and minimization Effectiveness of DILI risk communication Improving consistency of communications Unexpected DILI needs channels to collect and communicate information	
Monitoring	Restarting of therapy to be covered here (as opposed to rechallenge, to be covered by Group 1). Be careful when selecting the examples; make clear that they do not necessarily cover the main hepatotoxic products to look out for
Monitoring in patients on hepatotoxic drugs	
Monitoring to detect and manage hepatotoxicity of anti-cancer therapies	To be matched with Group 1's section on immunotherapy for cancer
Label discrepancies for hepatotoxicity risk warning and precautions for immunotherapy in non-oncological indications	
Detection and management of liver toxicity in patients treated with anti-TB and HIV drugs	
Risk management for herbal and traditional medicines	
Annexes: Glossary	Group 3 to extract definitions from all sections. See also previous CIOMS reports on related topics
Case report form (eCRF) for DILI	PDF for adaptation to companies' software. To be updated periodically; requires maintenance
Detailed info on Registries	
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