Council for International Organizations of Medical Sciences

Fifth meeting of CIOMS Working Group (WG) on Drug-Induced Liver Injury (DILI): 15–16 May 2019, Tallinn, Estonia

Minutes (web)

Version 7 June 2019

1. Opening

Hervé Le Louët (CIOMS President) opened the meeting and welcomed the participants. A list of participants is shown in **Annex 1**.

Meeting officers: The chairs and rapporteurs for the meeting were confirmed as follows:
– Chair: Hervé Le Louët; Co-chair: Arie Regev
– Rapporteurs: Maribel Lucena and Michael Merz, assisted by Monika Zweygarth.

Press coverage: Lembit Rägo (CIOMS Secretary-General) informed the WG about the information disseminated regarding the DILI group and its meeting, including: a press release[1], a 7-minute interview on an Estonian television show[2], and an interview session with a team of medical journalists on 15 May.

Expected way forward: Hervé Le Louët thanked the three subgroups for having produced comprehensive draft chapters, which will now be combined into one consistent, concise guidance document by an editorial team. The 5th WG meeting is therefore expected to be the last meeting of the full Working Group.

The target date for publication of the CIOMS DILI guidance is the end of 2019. The guidance will be made available on the CIOMS website as print copy and in PDF format. CIOMS will consider organizing some regional events to launch the guidance and promote its implementation. In addition, the WG may consider announcing the guidance in a journal article.

Meeting agenda and minutes of the 4th WG meeting: Printouts were handed out at the meeting. The agenda and the minutes of the 4th WG meeting (27-28 November 2018, Aix-en-Provence, France) were adopted.

[1] Available as slightly edited version (in Estonian) at: https://tervis.ohtuleht.ee/962743/sajad-ravimid-kahjustavad-maksa-kuidas-vahendada-ohtu-tervisele

[2] Terevisioon: https://etv.err.ee/935464/terevisioon, at 07:17-07:24 h

2. Updates on recent developments and cooperation with other initiatives

AASLD / FDA DILI Conference

Mark Avigan gave an update from the annual meeting co-hosted by the U.S. Food and Drug Administration (FDA) and the American Association for the Study of Liver Diseases (AASLD), held in Washington on 7-8 May 2019.[3] The meeting brought together DILI experts from academia, industry and government to discuss unresolved issues including: assessment of DILI in special patient groups such as those with pre-existing liver-disease and those with cancer, emerging tools to assess DILI risk, and areas in the FDA Guidance on DILI that may be in need of updating.

Pro-EURO DILI Net

Raul J Andrade presented an update from the Prospective European Drug-Induced Liver Injury Network (Pro-Euro DILI Net), a so-called "COST (Cooperation in Science and Technology) Action".[4] This network, which has five Working Groups, does not conduct its own research, instead it provides a platform for scientific and technical cooperation. The 1st Meeting of the Working Groups, the 2nd meetings of the Core Group and the Management Group, , and the 1st Training Course on *Assessment of Drug-Induced-Liver Injury: Key rules and common pitfalls. How to make a clinical narrative*, were all held concurrently in Malaga on 14-15 March 2019. The next meeting will take place in Palermo in October. Pro-EURO DILI Net will run for four years.

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).[5] IQ-DILI is composed of 16 member companies and to date has worked with over 30 academic and regulatory collaborators. Six working groups are active in Phase Ia; one paper has been published[6] and two are in preparation. Another seven working groups will start operating in Phase 1b. A Data Sharing Committee has been set up to oversee the establishment of a prioritized pilot project and roadmap for cross-company clinical data-sharing in Phase II.

Several other groups, such as the HBV Forum and TransCelerate Biopharma Inc, are also working to address DILI gaps. There is a strong need for communication and coordination between the groups to ensure consistency and harmonization, and to avoid conflicting recommendations.

HBV Forum guidance on liver safety assessment in drug development

Bob Fontana, co-chair of the HBV Forum sub working group on liver safety monitoring, spoke about the experience with producing a white paper on *Recommendations on liver safety assessment in HBV Drug Development.* This paper was developed by group of 12 experts collaborating by teleconference. An initial draft was proposed by a subgroup, and was then revised in line with suggested comments and edits from the full group. The paper will be finalized by 2-3 writers.

IMI2 TransBioLine project

Gerd Kullak-Ublick provided a brief update from the Translational Safety Biomarker Pipeline (TransBioLine) project funded by the European Commission's Innovative Medicines Initiative (IMI). It is coordinated by Michael Merz, with Guruprasad Aithal as academic lead of WP 2 Liver Injury along with Gerd Kullak as industry lead. Its five working groups focus on the development and regulatory

[3] https://www.aasld.org/events-professional-development/aasld-fda-dili-conference
[4] https://proeurodilinet.eu/
[5] https://www.iqdili.org/
[6] Regev A. *et al.* Consensus: guidelines: best practices for detection, assessment and management of suspected acute drug-induced liver injury during clinical trials in patients with nonalcoholic steatohepatitis. Aliment Pharmacol Ther. 2019 Mar;49(6):702-713. doi: 10.1111/apt.15153. Epub 2019 Feb 13.

qualification of new safety biomarkers, including liver safety biomarkers. The project was officially launched in February 2019 and will run for five years.

3. Progress reports from the subgroups

The Group Chairs presented progress updates on drafting of their chapters. In the lead-up to the meeting it had been suggested to start each section with a brief summary of its content and the recommendations, to facilitate the overall review of the guidance by the Working Group.

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

The drafts have undergone several rounds of revision. A new section has been drafted by Gerd Kullak-Ublick on using information from the pre-marketing phase to predict DILI post-marketing. An important part of this chapter 1 is the model Case Report Form ("e-CRF"), which will be presented separately in an electronically friendly format, and be summarized in the main text e.g. as a table.

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

Group 2 has produced an advanced draft, with each section preceded by a summary and recommendations. Section 2.6 (Postmarketing pharmacovigilance) will be reviewed together with information on this topic included in other Chapters with a view to combining some of this content.

Group 3: DILI risk stratification, risk minimization measures and risk communication
(Einar Björnsson)

Chapter 3 presents what is known about DILI risk, and how this is communicated in product information and patient leaflets for different types of medicines. Inconsistencies are highlighted. A detailed review of the labels of 21 oncology compounds will be made available as supplementary material. The Chapter will provide high-level recommendations and call for more research to generate needed evidence. It was agreed that recommendations about the use of the ICH Medical Dictionary for Regulatory Activities (MedDRA) is outside the scope of the CIOMS DILI guidance.

4. Plenary discussion

Audience: It was reconfirmed that the guidance should address all key stakeholders: regulators, industry and practising physicians, including non-expert clinicians who may report suspected DILI cases.[7]

Complementarity: It was noted that the added value of the CIOMS guidance will be to give a more global view. Particularly the proposed model Case Report Form for Hepatic Events could be a very valuable tool to harmonize reporting globally. The importance of promoting the dissemination and implementation of the CIOMS DILI guidance was re-emphasized.

[7] See also the 3rd WG Meeting minutes, page 2.

5. Group breakout sessions

On the afternoon of Day 1 and the second part of the morning of Day 2 the three groups worked in breakout sessions to work further on their drafts.

6. Plenary session: Presentation from China

In the morning of Day 2 Jia-bo Wang gave a presentation about Public-based ADR Reporting in China A free online system has been set up for the public to upload reports and request information about adverse reactions to drugs, including traditional Chinese medicines. The system is based on national regulatory data with currently more than 6.5 million ADR reports, and is monitored in real-time at national level. An English version will be launched during 2019.

The participants thanked Professor Wang for his presentation and discussed the value of patient-reported data to raise awareness on ADRs and enable signal generation, and the challenges of using such data in causality assessments.

7. Way forward

An editorial team had been selected at the 2nd WG meeting to oversee the final editing. For greater efficiency the size of this team was reduced from nine to five members, i.e. Arie Regev, Raul J. Andrade, Bob Fontana, Einar Björnsson and Mark Avigan, supported by Monika Zweygarth.

Next steps and timelines were agreed as follows:

- Group Leads: Work with group members to revise the draft chapter and send the revised drafts to the editorial team
  Arie Regev: Work on combining the chapters to complete the revisions, assure flow and reduce redundancy (end of June)
- Monika, in consultation with the editorial team: Combine the three draft chapters into a single well-structured document and circulate it to the WG (mid-August)
- WG members: Provide constructive comments to the CIOMS Secretariat (end of August)

Thereafter the editorial team will meet by teleconference to discuss the combined draft and the comments and recommend the way forward, including the possible need for another face-to-face meeting of the full group or the editorial team, at a date to be determined.

8. Concluding remarks

Hervé Le Louët thanked the WG members, the WG co-chair and the CIOMS Secretariat for their excellent contributions to the much-needed CIOMS guidance on DILI.

In a “tour de table” the WG members thanked CIOMS for convening this worthwhile initiative. They found the work professionally and personally rewarding and look forward to seeing it coming together in a final report. The members will stay in touch as needed during the editing process.

Lembit Rägo added his thanks to the WG members and reminded them of the current and future opportunities for collaboration in CIOMS Working Groups.

The meeting closed at 12:30 h.

Annex 1: Participants

CIOMS	Hervé **Le Louët**	APHP, CIOMS President
	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 (Day 1 only)
	Maribel **Lucena**	International Union of Basic and Clinical Pharmacology (IUPHAR)
	Yimin **Mao**	RenJi Hospital, Shanghai JiaoTong University School of Medicine, China
	Michael **Merz**	University Hospital Zurich, Switzerland
	Jia-bo **Wang**	Fifth Medical Center of Chinese PLA General Hospital (formerly Beijing 302 Hospital of China), China
Regulators	Mark **Avigan**	U.S. FDA
	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
Industry	Michele **Bortolini**	Roche
	Stewart **Geary**	Eisai
	Alexandre **Kiazand**	Astra Zeneca
	Gerd **Kullak-Ublick**	Novartis
	John **Marcinak**	Takeda
	Manfred **Oster**	Sanofi
	Xing Min **Qiu**	Pfizer
	Arie **Regev**	Eli Lilly
	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
	Uzu **Shinobu**	Pharmaceuticals and Medical Devices Agency (PMDA), Japan
	Monica **Soares**	ANVISA, Brazil
	Haibo **Song**	National Medical Product Administration (NMPA) (formerly called CDFA), China
	Jean-Marc **Vidal**	Formerly: European Medicines Agency (EMA)
Consortia	John-Michael **Sauer**	C-Path Predictive Safety Testing Consortium
Industry	Geoffrey **Ross**	Takeda – represented by John Marcinak
	Walter **Straus**	Merck