Council for International Organizations of Medical Sciences

Second meeting of the CIOMS Working Group on Drug-Induced Liver Injury (DILI)
14-15 November 2017, Málaga, Spain

Minutes (web)

Introductory session

Initiatives relevant to the CIOMS DILI WG, and the key contribution of the CIOMS WG, were briefly discussed:

IQ DILI

IQ DILI is an industry initiative under the umbrella of the IQ consortium. IQ overall has 42 member companies, 17 of which are represented in the IQ DILI group. IQ DILI is discussing best practices related to DILI in phase 1 of the project, and will focus on sharing data across member companies in phase 2. There is overlapping membership between IQ DILI and CIOMS DILI: nine experts are participating in both groups.

IMI2 TransBioLine

The call for a new IMI consortium called TransBioLine will likely be published by end of November. TransBioLine will focus on qualification of new safety biomarkers for drug induced liver, kidney, vascular, pancreas, and CNS injury. For liver, kidney, and vascular markers, the consortium is aiming at completing full regulatory qualification initiated by IMI SAFE-T, but also expanding application of the new markers to clinical practice. A strong focus will also be on evaluation of miRNA profiles for diagnosis of disease, so-called “liquid biopsies”.

Currently, applicant consortia are being formed to apply for participation in the call and funding by IMI. IMI selection of the winning consortium is expected in April 2018, consortium work will start by end of 2018/beginning 2019.

EASL DILI guidance

A guidance document on detection and assessment of DILI mainly in clinical practice, with some reference to drug development as well, is being prepared by EASL, due date is end of 2017. The document will include contributions from five CIOMS DILI WG members.

The CIOMS DILI initiative

The key feature differentiating the CIOMS DILI initiative from other efforts is inclusion of all key stakeholders in CIOMS, i.e. global regulators, academic Key Opinion Leaders, WHO and industry members, encompassing broad international participation (European, Eastern Mediterranean, African, South-East Asian and Western Pacific, and American) to capitalize on synergies and prevent redundancies.

Report content, structure and editing

The CIOMS DILI white paper will likely be an online publication. However, publishing the document as hard copy is feasible as well. The guidance will not have binding character, but may serve as foundation for future regulatory guidance, such as a potential corresponding ICH guidance.

In terms of content, structure, and editing of the CIOMS DILI paper, it was agreed to:

- Use standardized language for recommendations, e.g. “not clear yet” vs “to be considered” vs “recommended” vs “required”,
- Avoid overly prescriptive language,
- Have clear, brief boxed recommendations preceding each subsection,
- Ensure consistency, and a relevant, practical, homogeneous approach, considering this will be an open, ongoing process,
- Provide reasonable level of detail, highlighting weakness of data and knowledge gaps,
- Establish an editorial group to take care of compiling and aligning the main sections of the paper. Members of the editorial group will be CIOMS secretary, WG and subgroup chairs, Mark Avigan as regulatory representative, Walter Straus as industry representative, and both rapporteurs.

Professional writing support may be needed towards finalization of the document.

As for version control, it was suggested to avoid excessive editing in track changes mode, but rather have suggested edits included in comments in the document margin, and compile edits and comments regularly into tractable master versions.

The final document should be structured into:

- Introduction
  - Differentiate guidance from guideline
  - Describe general process
- Background
  - Key issues
  - Discussion
- Key recommendations

Discussion points from subgroup breakout sessions

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

Three key points were identified:

1. Summarize state of the art, reach consensus on key points
2. Causality assessment: RUCAM vs expert opinion, RUCAM not sufficient
3. Create CIOMS eCRF, discuss cut-offs for filling in CRF

Other points discussed:

- Separate development from clinical practice recommendations
- Industry and regulators will be key target audience
- Issue of duplicate data entry with associated data entry errors: to be solved at the company level
- TRANSCELERATE efforts on common standard protocols may help for CRF
- A data collection form for post marketing is not planned

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

The following points were discussed:

- Section structure: have summary synopsis/recommendation box, then text
- Ethics: foresee statement on newly identified risk factors
- New biomarker results from post marketing PV and controls from CT should go into a database to ensure dissemination of new relevant knowledge.
- Post marketing: take section on registries out into group 1, keep tables, write short section on biomarker sampling in registries
- Overlap with group 1: data elements, data capture form via LiverTox
- Can we recommend post marketing studies on a regular basis?
- Limitations of current registries: multicenter DILI registries are accruing biological samples to validate existing liver safety biomarkers and help identify new, improved biomarkers. However, these efforts are limited by the lack of pre-treatment and on-treatment samples and potential referral bias, emphasizing the need for prospective registries of patients in the general population taking drugs wherein biological samples are collected for future use pre-treatment, on treatment , and at the time of DILI onset.
- Should we recommend collecting baseline data (and samples??) at least for new drugs that have a signal already? Could this be done in health care provider groups such as Veterans Administration, or Kaiser Permanente in the U.S.?

Group 3: DILI risk stratification, minimization, and communication

The following points were discussed:

- Discrepancies across labels, oncology/immuno-oncology drugs
- Japan: often recommendation for liver test monitoring, more frequently than in US and Europe
- Look at monitoring practices across countries
- Optimal monitoring of drugs; learn from TBC treatment with clearly liver toxic drugs
- What about patients as target audience? To be considered at a later stage.
- Who is at risk? Define risk factors.

- Contextualize the risk based on clinical trial and post marketing data. Populations excluded from clinical trials: pregnant women, elderlies (sometimes)
- Clarify meaning of label language (e.g. "Use with caution"???)
- Define number needed to harm (NNH) to quantify and assess risk
- Risk management via REMS in the U.S. and RMP in Europe
- Harmonization is required: frequency, severity, risk factors and particularly if there are subgroups at increased risk.
- Effectiveness of monitoring as a risk mitigation strategy.
- Label recommendations: check after some years, decide on downgrading, use statin as example; or introduce new information released.
- Provide examples supporting these approaches.
- Use registries or similar, such as Veterans Administration (VA) data, to assess change in risk.

Place and date of next meeting

Post-meeting note: The 3rd meeting of the DILI Working Group was scheduled to take place in Reykjavik, Iceland, on 8–9 May 2018.

Participants

CIOMS	Hervé **Le Louet**	APHP, CIOMS President
	Lembit **Rägo**	CIOMS Secretary-General
Regulators	Mark **Avigan**	U.S. FDA
	Elmer **Schabel**	European Medicines Agency (EMA)
	Haibo **Song**	CFDA China
	Uzu **Shinobu**	PMDA Japan
	Monica **Soares**	ANVISA, Brazil
	James **Southern**	SAHPRA / Medicines Control Council South Africa
	Hajime **Takikawa**	Teikyo University, consultant of MHLW, Japan
	Mari **Thörn**	MPA Sweden
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)
	Michael **Merz**	University of Zurich, Switzerland
Industry	Michele **Bortolini**	Hoffmann La Roche
	Stewart **Geary**	Eisai
	Gerd **Kullak-Ublick**	Novartis
	John **Marcinak**	Takeda
	Manfred **Oster**	Sanofi
	Arie **Regev**	Eli Lilly
	Walter **Straus**	MSD
	Hui-Talia **Zhang**	Bayer

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