April 10, 2015

Dear Dr. Ma,

Please find attached the edited manuscript in Word format (file name: 16719\_revised.doc).

**Title:** Drug- and Herb-Induced Liver Injury: progress, current challenges and emerging signals of risk

**Author:** Emanuel Raschi, Fabrizio De Ponti

**Name of Journal:** *World Journal of Hepatology*

**ESPS Manuscript NO:** 16719

***1. Revision has been made according to the suggestions of the reviewers. A point-by-point responses is provided below. Q denotes Question; A denotes Answer.***

**Reviewer # 02861277.**

*General comment.* The authors provided a very meticulous overview of the literature concerning drug- and herb-induced liver injury (DILI and HILI). At the present, DILI and HILI represent a very attractive research field given the multidisciplinary approach as well as the strict association with the increasingly required multi-drug therapies, athletic performances and the worldwide spreading of the alternative medicine usage. Overall, the manuscript covers most of the aspects related to DILI and HILI; however, I believe that some of them should be much more argued.

*Q1.* Is there an association between gender and DILI and HILI?

*A1. Patient gender and age are considered to be risk factors for liver injury, although the relationship is not straightforward. This is the main reason why we did not address this aspect in the previous version. In the revised version, we have discussed this issue in the section “epidemiology”, also by quoting recent publications (Petronijevic et al. J Clin Pharmacol 2013 Apr;53(4):435-43; Hunt et al. Regul Toxicol Pharmacol 2014 Nov;70(2):519-26).*

*Q2.* In order to obtain a compelling publication, the authors should provide some hint concerning the molecular mechanisms involved in pathogenesis of DILI and HILI (liver metabolism of the drugs, oxidative stress, protein modifications and immune responses induction). Overall, on this line, could be the anti-oxidant treatment the first choice to prevent acute liver failure during DILI?

*A2. As suggested, we have briefly described major mechanisms involved in the pathogenesis of liver damage, discussing relevant clinical implications. A paragraph is now provided, called “risk factors and pathogenesis”. We decided to keep this aspects within a reasonable length because this is not the focus of this manuscript.*

*Q3.* Moreover, I believe that the authors should cite the very recent Bjornsson’s publication sharing most of the information reported in present manuscript. Bjornsson ES. Drug-induced liver injury: an overview over the most critical compounds. Arch Toxicol 2015 Jan 25. DOI 10.1007/s00204-015-1456-2 PMID: 25618544.

*A3. We thank the reviewer for this suggestion. We quoted the recent paper by Bjornsson where appropriate.*

**Reviewer # 02861401.**

*General comment.* This review paper provided a wide overview of the current clinical status of drug- and herb-induced liver injury (DILI and HILI). It also provided some general recommendation to clinicians in dealing with potential DILI and HILI. It seems that the authors attempt to cover most important clinical areas related DILI and HILI. However, it seems that this review paper only touched the surface and more details are really needed for specific areas.

*Q1.* For example, the current understanding of the potential mechanisms of DILI and HILI should be discussed in details.

*A1. As suggested by reviewers, we have briefly described major mechanisms involved in the pathogenesis of liver damage, discussing relevant clinical implications. A paragraph is now provided, called “risk factors and pathogenesis”. We decided to keep this aspects within a reasonable length because this is not the focus of this manuscript.*

*Q2.* Current efforts in measuring and interpreting DILI and HILI and the detail challenges in making correct early diagnoses should also be discussed.

*A2. We emphasized these aspects, also by quoting recent publications.*

*Q3.* The efforts of liver toxicity knowledge database should also be discussed.

*A3. We have discussed achievements of this project, especially in the last paragraph devoted to “existing consortia”.*

**Reviewer # 02861276.**

*Q1.* The title is clumsy and inaccurate and needs to be altered to be more accurate.

*A1. The title was modified by emphasizing the post-marketing setting, which is one of the key aspects of the paper.*

*Q2.* The clinical data are incomplete.

*A2. We have now provided, in the clinical section, additional details based on the recent American guideline.*

*Q3.* What is the aim of the study for clinical therapy?

*A3. In the revised version, we have attempted to cover the issue of management of DILI, by quoting recent publications. Please remember that this is a minireview and its focus is to highlight important emerging issues. The aspect mentioned by the referee is duly covered by the quoted American guideline.*

**Reviewer # 02861333.**

*General comment.* In this review study, the authors summarized the DILI and HILI diagnosis, differential diagnosis, treatment and, more special aspect, emerging signals of risk. The study gives many new data and publications focused on these two diseases.

*No answers to specific issues raised by the reviewer are required.*

***2 References and typesetting were corrected. Twenty-two new references have been added to fulfill request by reviewers.***

Thank you again for considering our manuscript in the *World Journal of Hepatology.*

Sincerely yours,



Fabrizio De Ponti, MD, PhD

Pharmacology Unit - Department of Medical and Surgical Sciences - University of Bologna

Via Irnerio, 48

I-40126 Bologna BO

Italy

Tel.: +39-051-2091805

Fax: +39-051-2091780

e-mail: fabrizio.deponti@unibo.it