Final Concept Paper
M12: Drug Interaction Studies
Dated 17 November 2019
Endorsed by the Management Committee on 18 November 2019

Type of Harmonisation Action Proposed

Type of action: A new harmonized guideline
Category: Multidisciplinary

Statement of the Perceived Problem

Drug-drug interactions (DDIs) can occur when patients are taking more than one drug. It is impractical to evaluate every drug combination in clinical trials during the development of investigational products. Hence systematic, risk-based approaches are used to assess DDIs during therapeutic product development. Although regulatory agencies use risk-based strategies, there are some differences among agencies in the approaches used. Different regulatory agencies may require different in vitro and clinical DDI studies be conducted based on the specific regional approach. In addition, different study design recommendations for DDI studies can lead to differences in interpretation among agencies or requirements for additional studies. There are also inconsistent approaches to the determination of clinical significance of DDI study results and the reporting of results and recommendations in the product labeling.

If harmonization does not occur, regional heterogeneity will continue to add burden to the pharmaceutical industry because they have to meet varying expectations from the different agencies. This burden may not only delay patient access but also may result in heterogenous recommendations pertaining to the use of new therapeutic products with concomitant medications.

Issues to be Resolved

The DDIs of interest for this harmonization effort are PK-driven and mediated by drug metabolizing enzymes and transporters. A summary of main technical and scientific issues that can be addressed via harmonization:

- **In vitro studies** - The purpose of in vitro studies is to inform the need for conducting clinical DDI studies. However, the criteria to inform the need for subsequent clinical DDI studies is different across the global regulatory agencies, potentially leading to disharmonious recommendations. For example, there are discrepancies for the criteria used to predict in vivo DDI potential mediated by induction or time-dependent inhibition of CYP enzymes and inhibition of transporters. There is also lack of consensus on how to assess the DDI potential of metabolites. Achieving harmonization on the considerations for the in vitro methods utilized for screening DDI potential and the criteria used for determining the need to perform clinical DDI studies will lead to more consistent regulatory expectations for clinical DDI studies globally.

- **Clinical DDI studies –** The design and conduct of clinical DDI studies as well as interpretation and reporting of the study results lead to essential information in product labeling**.** In this context, there is a need to develop a generally agreed upon list of substrates, inhibitors or inducers of major CYP enzymes and, where feasible, probe substrates or inhibitors of major transporters to be used in clinical DDI studies. Such effort will harmonize expectations from the different regulatory agencies on drugs that can be used in global clinical DDI studies and help with interpretation of the clinical implications. Further, there is a need to develop a consistent approach to determination of clinical significance of DDI study results and the reporting of results.

  Pharmacogenetic studies have been utilized to delineate the role of certain enzymes and transporters in the pharmacokinetics of investigational drugs and inform the DDI effect. There is a need to reach agreement on the applicability of pharmacogenetic results (e.g., in lieu of dedicated DDI studies) and considerations for conducting pharmacogenetic studies.

- **Physiology-Based Pharmacokinetic (PBPK) Approaches** – To the extent possible, the guideline will further explore the application of PBPK modelling approaches to assess clinical drug-drug interactions. Although a consensus on best practices for conducting such assessment is needed, developing consensus in this area will likely be very intensive and require a separate dedicated workforce.

Background to the Proposal

Different regional regulatory agencies have published guidances to assist drug developers in the evaluation of DDI potential during drug development [References 1-4]. However, no international DDI guidelines exist. This Topic Proposal provides an opportunity for the regulatory agencies to share their knowledge, experiences, and general expectations. The effort will lead to a global harmonization on the topics where there are some local consensuses already.

Perspectives on risk/benefit vary across regulatory authorities. However, harmonization across the different regulatory agencies on if and when a clinical DDI study needs to be performed, study design considerations, and results interpretations can help reduce uncertainty for the pharmaceutical industry and allow them to use a more global approach to assess DDI liabilities of their drugs. This will lead to more efficient utilization of resources and help bring drugs to the global market more quickly for the patients who need them.

References:

1. FDA, United States: Draft Guidance for Clinical Drug Interaction Studies, 2017: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf
2. FDA, United States: Draft Guidance for In Vitro Metabolism and Transporter Mediated Drug-Drug Interaction Studies Guidance for Industry, 2017: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM581965.pdf
3. EC, Europe: EMA Guideline on investigation of drug interactions, 2012: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/07/WC500129606.pdf

4. MHLW/PMDA, Japan: Guideline on drug interaction for drug development and appropriate provision of information, 2018 : https://www.pmda.go.jp/files/000228122.pdf

Type of Expert Working Group and Resources

The EWG should include experts in the field of pharmacokinetics and clinical pharmacology with experience in DDIs assessments and interpretation.

Timing

Given the state of knowledge in the field, it is the appropriate time to start developing a harmonized guidance by seeking input from the broader ICH Members. It is estimated that it would take 3-4 years to develop and finalize a harmonized guidance.