30.06.17

Submission of comments on *Concept paper on a revision of the guideline on the investigation of drug interactions – EMEA/CHMP/694687/2016*

Comments from:

| Name of organisation or individual |
| --- |
| EFPIA – Sandra Rodrigues (sandra.rodrigues@efpia.eu) |

*Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.*

*When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).*

1. General comments

| Stakeholder number  *(To be completed by the Agency)* | General comment (if any) | Outcome (if applicable)  *(To be completed by the Agency)* |
| --- | --- | --- |
|  | In consideration of the expansion of the scientific knowledge and experience since the implementation of the Guideline on the Investigation of Drug Interactions (2012), the highlighted scope of the concept paper is appropriate.  Any efforts to harmonize regional expectations (e.g. EMA, FDA and PMDA), as far as possible, would be supported. |  |
|  | Regarding model systems required for MDR1 inhibition. Is it necessary to use two different transvectorial transport cell model systems or do we now have developed our understanding to use only one? Clarification in the draft guideline would be welcome. |  |

1. Specific comments on text

| Line number(s) of the relevant text  *(e.g. Lines 20-23)* | Stakeholder number  *(To be completed by the Agency)* | Comment and rationale; proposed changes  *(If changes to the wording are suggested, they should be highlighted using 'track changes')* | Outcome  *(To be completed by the Agency)* |
| --- | --- | --- | --- |
| Line 24  (Inhibition and induction of enzymes in the intestine: specifying cut offs for poorly soluble drugs) |  | **Comment:** To assess the estimated gut concentration we recommend that EMA consider other approaches, beyond ‘dose/250 mL’, when the dose is not soluble in 250 mL, (e.g. simulated intestinal fluids (fed conditions) for any calculation.  This would represent the worst case scenario as the intracellular concentration is subject to modulation by the passive permeability of the test inhibitors. |  |
| Lines 25-26  (Specific in vitro study design recommendations for in vitro induction studies: number of concentrations to study) |  | **Comment:** The current EMA DDI guideline recommends *“At least three different concentrations should be used.”* We agree that three different concentrations would be the adequate to show the absence of induction (<2-fold increase in mRNA and <20% of the response of positive controls). If induction parameters are being determined, the in vitro induction study should include enough concentrations of the test inducer to adequately describe the concentration-response curve to best obtain the EC50 and Emax values. Obtaining the appropriate concentrations of inducer in the in vitro study would be dependent upon test inducer solubility and cell viability particularly with inducers with high EC50 values. |  |
| Line 27  (Transport as rate limit for elimination: in vivo study design considerations) |  | **Comment:** It is important to understand whether active transport is the rate limiting step for the elimination of drugs, which could be assessed via mechanistic clinical DDI studies. However, this should be restricted to the transporters, such as OATP1B, which have well established literature data and validated study approaches.  If EMA has sufficient internal data, it would be helpful to give some guidance (e.g. a table summarizing examples of specific inhibitors for each transporter to separate liability of transporter-mediated DDI from metabolism).  The importance of clearly presented in vitro data describing the overall DDI potential is acknowledged and critical to the assessment of an application. However, given differences in criteria across key global agencies, the format of presentation has to be left to the discretion of Applicants.  **Proposed change (if any):**  Rather than a templated table(s) or other specification(s), guidelines for the data and supporting details expected in support of regulatory filings regarding the in vitro/in vivo evaluation of the DDI potential should be clarified. An example of a table(s), perhaps separately for in vitro and in vivo data, may be reasonable for general guidance; however, this tabulation should not be mandated with Applicants given the flexibility in the method of presentation.  Clinical microdosing studies (Prueksaritanont et al Clin Pharmacol Ther. 2017,101(4):519-530; Maeda et al. Clin Pharmacol Ther. 2011, 90(4):575-81) can be applied as a mechanistic approach to identify the rate-limiting step of hepatic uptake vs. metabolism. In such a case, if PK data of clinical probes in microdose have been validated to be extrapolated to the therapeutic dose, dedicated clinical DDI studies with individual probes at therapeutic dose may not be needed and would benefit from clarification in revisions to the current 2012 Guideline. |  |
| Line 28  (The addition of a table to present in vitro drug-drug interaction (DDI) information) |  | **Comment**: We agree that a table format would be useful to summarize the outcome from all static model DDI predictions. In addition to static modelling predictions, it would be beneficial if the agency was open to looking at a table summarizing the outcome from any PBPK modelling that the sponsor may have conducted.  Any table should include unbound Ki or KI values or fumic for those values for CYP enzyme DDI. It would also be of value to have the static predicted “R” value and mechanistic modelled (static or PBPK) AUCR value to put the in vitro DDI information into perspective with the clinical exposures. |  |
| Line 29-30  (Specifying a cutoff (two-fold) for the inhibition constant ‘Ki’ shift to conclude mechanism based inhibition, including details regarding the pre-incubation duration) |  | **Comment:**  There are compounds that are known to be time-dependent inactivators (TDI) that have shown IC50 shifts (not ‘Ki shift’) of ≥1.5 with a 30-min preincubation (Berry and Zhao 2008 *Drug Metab Letters* 2:51-59), this suggests the use of such values as a cut-off for identifying a compound as a TDI.  It is suggested that other assays such the “loss of activity” or “kobs” assays as other options for an initial TDI screen (Wong et al., 2016 Xenobiotica, 46:11, 953-966 and Zimmerlin et al. (2001) *Drug Metab Dispos* 39:1039-46) should be used. The “loss of activity” assay (% inhibition at 30 min, 10 uM) was found to be a good predictor of in vivo DDI and had a low potential for false negatives or positives. Cut-off values are proposed in each of the publications.  The preincubation duration is recommended to be 30 min (Grimm et al., 2009 *Drug Metab Dispos* 37:1355–1370).  **Proposed change (if any):** Terminology change from Ki to IC50. The preincubation duration is recommended to be 30 min (Grimm et al., 2009 *Drug Metab Dispos* 37:1355–1370). |  |
| Line 31  (In vitro induction screening: update on study design recommendations) |  | **Comment:** It may be premature to update the current guidance for in vitro induction screening. Literature data is only now emerging on how measured concentrations may impact EC50 values.  More clarity is requested around the term “negligible” (pg.22 of the current DDI guidance), with respect to compound loss in in vitro induction assays.  *“Unless loss due to in vitro drug metabolism, degradation or lysosomal trapping of drug during culture conditions has been shown to be negligible, or if the loss has been quantified in the system prior to the induction assay and compensated for through the amount of drug added /medium change interval, measurements of concentration of parent drug in the medium are encouraged at several time points the last day of the incubation”.*  We believe it would be useful to define what is meant by “negligible” loss. For example, ‘<50 % of test article lost from the media at end of the last day of treatment’ may be a useful guideline.  Incubation durations for the induction study are typically 2-3 days, as surveyed across Pharma Co. (Chu et al., Drug Metab Dispos 2009 37:1339–1354). Particularly for mRNA measurements, positive control responses are more than adequate at 48h of treatment. Treatment durations of 72h do not appear to offer a better mRNA induction response over 48h (Zhang et al., *Drug Metab Letters* 2010 4, 185-194).  In addition, three days of incubation is not consistently achievable using cryopreserved primary hepatocytes. The EC50 for CYP3A4 induction by rifampin is 0.66 uM (Fahmi et al., DMD, 2016). Rifampin concentrations used as positive control should be 10 uM (15 –fold above EC50). Higher rifampin concentrations can diminish the rifampin induction response exhibiting a bell shaped curve.  **Proposed change (if any):**  Revise the length of incubation of investigational compound from 3 days to earlier time points.  The positive controls used should be as selective as possible and be chosen based on current scientific knowledge. Rifampicin (***10***μM) is recommended as positive control for PXR, CITCO (≤100 nM) ***or phenobarbital (≥500 µM)*** for CAR, omeprazole (50μM) for the Ah-receptor and dexamethasone (50μM) for GR.  It is proposed that the positive control rifampicin be used at a concentration of 10 µM as CYP3A4 should be maximally induced at this concentration with an EC50 of ~ 1 µM (Einolf et al., 2014 Clin Pharmacol Ther 95:179-88 Supplemental Table S1) and also to be consistent with the FDA guideline.  Even though phenobarbital is an indirect activator of CAR, it should suffice as a positive control for activation through the CAR receptor.  If induction through PXR/CAR activation is indicated *in vitro*, an *in vivo* induction study should be performed investigating the effect on CYP3A  For the concentrations of test inducer to study, limitations due to solubility and cell viability should be acknowledged in the guidance.  Lastly, if an in vivo induction study for CYP3A4 is warranted based upon in vitro induction and use of modelling (basic method or more mechanistic models) and if the test drug is also a CYP3A4 inhibitor, an induction study with another inducible enzyme such as CYP2C would not be helpful in understanding the test drug’s ability to induce CYP3A4. It is proposed not to run an in vivo study with a CYP2C substrate as the magnitude of induction of CYP2C is not relevant to the induction magnitudes obtainable for CYP3A4. |  |
| Line 32-33  (Transporter inhibition screening: update of the list of transporters to screen from a 32 pharmacokinetic perspective). |  | **Comment:** It is believed that the current guidance covers the transporters that are relevant targets for pharmacokinetic drug-drug interactions based on the current knowledge. Additional transporters should be evaluated on a case-by case basis based on available information on the mechanism of action of the test drug or established structural activity relationships.  **Proposed change (if any)**: The interpretation of clinical DDI data related to the inhibition of OCT1 can be complicated by non-selective inhibition of other transporters (e.g. OCT2 and MATE1/2K); therefore, evaluation should be restricted to the setting of potential concomitant medication with metformin. Based upon the current knowledgebase, we do not believe that there is sufficient scientific characterization or evidence of clinical significance to merit screening of OATP2B1 and OAT2 for general consideration and these continue to be evaluated on a case by case basis.  We propose that Bile Salt Export Pump (BSEP) be deleted from the screening list considering the clinical translation of in vitro BSEP inhibition has not been clearly established and BSEP inhibition in vivo may not result in a direct translation to an increase in serum bile salts. We propose that the sponsor only study BSEP if there are liver safety signals. |  |
| Line 34-35  (Transporter inhibition screening: update of some cutoffs for determining in vivo relevance of in vitro inhibition). |  | **Comment:**  As different cut-off values are being used by EMA, PMDA and FDA to determine the in vivo relevance of transporter inhibition, we would recommend EMA consider cut-off values proposed by these agencies if the guidance is updated and that it investigates additional approaches to attain some form of cross-agency harmonization where appropriate.  In the current guidance cut-off values for transporters are based on historic clinical DDI study results and in vitro inhibition data coming from different labs. For efflux transporters large variability in vitro inhibition data has been described. Especially if different assay types are selected (cellular vs inside-out vesicles) the obtained Ki values might be different if experimental design and parameter calculations are not adequately selected. Therefore, current cut-offs might trigger unnecessary clinical studies or might even not be conservative enough.  It is therefore recommended to allow the generation of assay- and lab-specific cut-offs. The new guidance might define criteria for the conduct of cut-off generation (e.g. number of compounds for the assessment, statistical methods and expectations, accepted clinical reference data). Following this approach, the requirement of investigation Pgp inhibition in two different assays systems (DDI guideline page 27) should be not be necessary any longer.  Also when using R-value/liver inlet concentration cut offs by Vaidyanathan et al. (J Clin Pharmacol. 2016 Jul;56 Suppl 7:S59-72), consider also the following:  - For NCEs that cannot be tested to high enough concentrations *in vitro* due to solubility limitations; need for clinical interaction studies in situations where inhibition was not observed *in vitro* at the highest soluble concentration, as the concentration of the NCE would also be solubility limited *in vivo.*    -the recommendation to use Ki values; IC50 is more readily determined and values are similar when the probe substrate is at a concentration well below the Km, as per the Cheng-Prusoff equation (Ki = IC50/(1+[S]/Km) (Brouwer et al, Clin Pharmacol Ther. 2013;94(3):412).    **Proposed change (if any):** In the revised draft guideline, please consider replacing Ki determination for transporters with IC50 |  |
| Line 38-39  (The need to know whether the (unbound) target concentration was maintained in an in vitro system during the incubations) |  | **Comment:**  We believe it is important for the sponsor to have a good understanding for each in vitro assay whether the compound stability/physicochemical properties (e.g. metabolism, solubility, non-specific binding) will have any meaningful impact on data interpretation.  We do however welcome further discussion on this important topic as experience demonstrates that many NCEs are poorly soluble in *in vitro* assay buffers and/or have high levels of non-specific binding to the cells/cell fractions/assay plates.  Particularly for DDI studies using HLM, fumic can be measured.  It should be expected that the Ki values obtained from this system are unbound values; otherwise the DDI could be under-predicted. In addition, a sufficient percentage of the initial test inhibitor compound concentration should be present at the end of the incubation period to ensure appropriate exposure of the inhibitor,  For in vitro induction studies, it is reasonable to monitor the amount of test drug in the media to ensure adequate time of cells exposed to a particular concentration of the drug. In turn, one may be able to reference previous metabolic stability assessments from pooled human hepatocytes to assess the amount of test compound likely to be remaining over a 24h period. |  |
| Line 40  (The use of Bile Salt Export Pump (BSEP) inhibition data). |  | **Comment**:  We are in agreement with recommendations by the International Transporter Consortium that measuring inhibition of BSEP is useful for compounds that cause cholestasis there is an association between drug-induced BSEP inhibition and liver injury in humans, causality has not been well established (Hillgren et al. Clin Pharmacol Ther. 2013. 94:52–63) However, while there is an association between drug-induced BSEP inhibition and liver injury in humans, causality has not been well established; therefore, we consider that the recommendation to measure inhibition of BSEP for clinical candidates is premature, as and that additional data are needed before interpretation of data is feasible, as detailed below.  Evaluation of BSEP inhibition in membrane vesicles has yielded a high degree of false positives (Dawson et al., Drug Metab. Dispos. 2012. 40, 130–138, Morgan et al. Toxicol. Sci. 2010. 118, 485–500) and thus further evaluation of compounds predicted to inhibit BSEP in a hepatocyte based system is warranted. For instance, one company has identified dipyridamole as a potent inhibitor of human BSEP, but no inhibition of bile salt transport was observed in a micropatterned hepatocyte model. This discrepancy was likely explained by the rapid metabolism of dipyridamole to a glucuronide.  Additionally, there is no consensus on the relevant drug exposure parameter to use to put the in vitro inhibition data into context. The use of unbound liver inlet concentration (as calculated in Hirano et al. DMD. 2006. 34, 1229-1236) is appropriate for non-substrates of liver uptake transporters but unbound intracellular concentrations may need to be considered for substrates of liver uptake transporters. In addition, it remains unclear whether BSEP inhibition alone can cause cholestasis or whether inhibition of other mechanisms are needed to induce cholestatic liver injury (e.g. inhibition of basolateral efflux transporters such as MRP3/4 and OSTα/β, and FXR antagonism).  An in vivo assessment of BSEP inhibitors remains challenging as confounding factors (e.g. inhibition of bile salt uptake or bile salt synthesis) make data interpretation difficult if increases in plasma levels of bile salts are found. Further, there is no consensus on whether animal models can help to understand the risk for BSEP-mediated cholestasis nor is there an alignment on biomarkers to measure and how to translate the results obtained with these biomarkers to humans as there are species differences in bile salt composition and transporters (e.g. OSTa/B is expressed in human but not in rat liver). In the case where a BSEP inhibitor would be tested in the clinic, there is no consensus on the appropriate study design and which biomarkers should be measured.  In the current guidance cut-off values for transporters and metabolic enzymes calculated as the ratio of the measured or anticipated human plasma concentrations at a relevant clinical dose and the in vitro inhibition potential (Ki) of a perpetrator drug. This approach follows the concept of the free-drug hypothesis, assuming complete and rapid equilibration of the unbound drug in plasma and in the target tissue.  However, emerging data reveal that liver-to-blood concentration ratio of the unbound drug (Kp,uu) may significantly deviate from unity in organs with active metabolic and transport activity such as the liver. In a recent study the frequency of drug-induced cholestasis (DIC) was successfully estimated using unbound intrahepatic calculations and BSEP in vitro inhibition data (Riede et al, 2017. *Drug Metab Dispos*;45:523-531). Based on in vitro Kp,uu, the unbound intracellular concentrations were up to 14-fold different compared to those unbound in the plasma. A clear separation of drugs, which are not implicated with DIC was observed for a cut-off of 500-fold (BSEP IC50 and unbound intrahepatic concentration). It is therefore recommended to perform risk assessments that take into consideration the unbound intracellular drug concentrations and to expand the datasets that are currently available in order to further refine the cutoff values.  Overall, the clinical translation of in vitro BSEP inhibition has not been clearly established. BSEP inhibition in vivo may not result in a direct translation to an increase in serum bile salts. We recommend BSEP be deleted from the list of transporters to be investigated until such translation is well established and propose that the sponsor only study BSEP if there are liver safety signals. |  |
| Line 41  (How to calculate the unbound inlet concentration). |  | **Comment:** The current approach to calculate unbound inlet concentration (Hirano et al. (DMD. 2006. 34, 1229-1236.) is considered to be very conservative.  The calculation of the unbound inlet concentration has been described in the following manuscript:  Ito et al., (1998) Pharmacol Rev 50: 387-411 (Equation 22 in the publication)  Proposed change (if any): The use of measured or predicted Ka and FaFg should be considered for development compounds where human PK data exists. |  |
| (How to verify adequate sensitivity of the system for in vitro induction studies) |  | **Comment:**  Variability in the in vitro induction response could preclude a 2-fold induction cut-off as indicative of a positive response.  The sensitivity of the in vitro induction study would be defined by the positive control inducers used at the concentration at the Emax for the particular enzyme being evaluated. The positive control inducer should induce mRNA and activity at least ≥5-fold to capture an induction response within 40% of the positive control (i.e. 2-fold change by the test compound when positive control is at 5-fold). |  |
| Lines 44-45  (How to present the mass balance study results: adding a recommendation on how to illustrate the elimination of a drug schematically) |  | **Comment:**  The importance of clearly presented mass balance information for victim DDI assessments is acknowledged. While a schematic illustration of mass balance results may be beneficial for presentation in the dossier to assist in the review of the application, this may be overly prescriptive for the purposes of product labelling.  Examples of how such an optional scheme could look are shown below:      We prefer that the precise method of presentation of results in both the dossier and labelling be left to the discretion of individual applicants. |  |
| Line 46 |  | **Comment:** Currently the text pertaining to the necessity of in vivo evaluation for effects on contraceptive steroids if a potential teratogen is intended for use in fertile women, regardless of the *in vitro* induction study results is harmonized across the EMA (2012) and FDA DDI (2012) Guidance documents.  **Proposed change (if any):** If any changes are proposed to the EMA DDI Guideline, these should be considered together with the expectations of the FDA PLLR to maintain harmonization of intent, as far as possible, across these Global Guidelines. |  |
| Line 47 |  | **Comment:** The duration of treatment of a test inducer to measure CYP3A4 induction in vivo would be compound specific. Considerations should be made for the time the compound takes to reach steady-state and the time for induction of the target enzyme (dependent on the degradation/synthesis rate constant of the induced enzyme, kdeg). |  |
| Additional Topics |  | **Comment:** To avoid overly prescriptive selection criteria, the examples provided in the lists of in vitro substrates and inhibitors as well as in vivo substrates and inhibitors across Appendices IV-VII of the current 2012 Guideline were not meant to be inclusive of all possible in vitro or clinical probes for evaluation.  **Proposed change (if any):** Given the expansion of the knowledgebase and formulary, we recommend updates and additions, beyond that identified in Line 32, to lists of in vitro and in vivo substrates, inhibitors and inducers. This may include lists, classified by potency (e.g. strong, moderate, weak), as appropriate, for in vivo inhibitors and inducers of drug metabolizing enzymes, as well as examples of in vivo inhibitors, inducers and substrates of transporters. |  |
| Additional Topics |  | **Comment:** Section 5 (Pharmacokinetic Interactions); pp. 7/59 of the current Guideline states “In the area of HIV there have been cases of unexpected interactions. When developing a drug in such an area, in vivo interaction studies should be considered with commonly combined drugs having a relatively narrow therapeutic window while more knowledge is gained on the mechanism behind the unsuspected interactions in the field”.  **Proposed change (if any):** It remains unclear what the definition and criteria for these “unexpected interactions” may be and examples for which in vivo studies would be expected or those settings whereby interactions could be suitably discharged with other modalities (e.g. PBPK). |  |
| Additional Topics |  | **Comment:** Revisions to the FDA draft DDI Guidance Document are also planned and in consideration of the breadth of the in vitro and in vivo topics reviewed, the intent of these updates may also include issuance of separate documents for in vitro and in vivo evaluations of the DDI potential. Should EMA consider similar efforts to separate in vitro from in vivo DDI guidelines, EFPIA would be supportive. The proposed revisions to the labelling topics in the current DDI Guideline could be incorporated together with topics pertaining to in vivo content or within a separate Guideline highlighting the expectations of labelling across Clinical Pharmacology content and relevant SmPC sections. |  |
|  |  |  |  |

Please add more rows if needed.