

Concept Paper

S1: Rodent Carcinogenicity Studies for Human Pharmaceuticals

Dated and endorsed by the Steering Committee on 14 November 2012

Type of Harmonisation Action Proposed

A change to the current S1 harmonized Guidelines on rodent carcinogenicity testing is proposed to be published through the ICH process. Change is needed in order to introduce a more comprehensive and integrated approach to addressing the risk of human carcinogenicity of pharmaceuticals. This change is also expected to clarify and update, without compromising safety, the criteria for deciding whether the conduct of a two-year rodent carcinogenicity study of a given pharmaceutical would add value to this risk assessment. This initiative is driven by the retrospective analyses of several data sets reflecting three decades of experience with such testing. The specific S1 Guidance modification and harmonization action will deliver the desired change while seeking to minimize modification to existing guidance, and will be more crisply defined as public comments and prospective data are received.

Statement of the Perceived Problem

The three current ICH Guidelines, namely S1A the Need for Long-term Rodent Carcinogenicity Studies of Pharmaceuticals, S1B Testing for Carcinogenicity of Pharmaceuticals, and S1C(R2) Dose Selection for Carcinogenicity Studies of Pharmaceuticals provide recommendations on which pharmaceuticals warrant carcinogenicity testing, appropriate approaches for evaluating carcinogenicity potential, and appropriate dose selection, respectively.

The current S1A Guideline discusses the criteria used to determine whether an evaluation of the carcinogenic potential of a pharmaceutical is considered necessary. The S1A Guideline treats pharmaceuticals differently based on duration of exposure, *a priori* concern about carcinogenic potential, and clinical indication. However, among pharmaceuticals that require evaluation of carcinogenic potential, S1A does not provide guidance on experimental strategies that could appropriately evaluate the carcinogenic risk presented by a given pharmaceutical.

On the other hand the current S1B Guideline discusses the experimental approaches intended to assess carcinogenic potential of a pharmaceutical when such an evaluation is indicated by the criteria discussed in S1A. The S1B Guideline effectively treats pharmaceuticals equally in recommending that all drugs needing carcinogenic assessment be evaluated in a two-year rat bioassay and a two-year or shorter term mouse bioassay. The S1B Guideline does not discuss the potentially important contribution that aspects of the pharmacology and toxicology of a given pharmaceutical might provide in terms of identifying the degree of carcinogenic risk or in modifying an investigational approach suitable to address that risk beyond the standard two-year bioassay. The carcinogenic evaluation of a pharmaceutical expected to induce tumors, for example, based on its known pharmacological or toxicological actions, might not be further informed by conducting two-year bioassays if sufficient evidence exists from relevant endpoints in shorter term studies.

Guidance is needed therefore, from an Expert Working Group (EWG) to help determine whether aspects of a pharmaceutical's pharmacology and toxicology, as currently evaluated in nonclinical programs, can be used to adequately assess the degree of carcinogenic risk short of conducting two-year rodent bioassays. The EWG will investigate whether alternative or additional testing strategies to the current approach could enhance assessment of carcinogenic risk of pharmaceuticals. These activities will enable the EWG to address and clarify the conditions under which two-year bioassays will either add value or not add value to an assessment of a pharmaceutical's carcinogenic potential. This work is expected to strengthen the testing strategy

for predicting human carcinogens, and lead to a reduction in the number of two-year rodent bioassays.

Proposal

It is expected that this proposal will modify the ICH S1 rodent carcinogenicity testing Guideline, by advancing an approach in which the need for 2-year bioassays are not automatically triggered, but evaluated instead based on a case-by-case approach taking both predicted positive carcinogenicity study outcomes as well as negative outcomes into consideration for a scientifically justifiable waiver.

It is proposed that knowledge of pharmacologic targets and pathways together with toxicological data can provide preliminary characterization of the carcinogenic potential of some pharmaceuticals sufficient to determine whether the conduct of two-year rodent bioassays would add value to that assessment.

The scope of data necessary to preliminarily assess the carcinogenic potential of new compounds, and whether two-year studies would add value, will require extensive definition, and would be a major focus of the EWG's activity. Pivotal considerations to a preliminary carcinogenicity assessment might include criteria such as the genotoxicity profile, evidence of 'histologic risk factors of neoplasia' in chronic toxicology studies, and evidence of hormonal disruption. These criteria will need to be well-defined and consistently applied, but it is recognized that these endpoints must be considered in assessing carcinogenic risk of any pharmaceutical. Other pivotal considerations would include primary and secondary pharmacology, known drug class effects and nonclinical and clinical experience with the drug class, and the degree to which the rodent models the human in terms of pharmacology, PK/ ADME, and, if known, human toxicology of the pharmaceutical in question. A global harmonized process may be needed for regulatory agencies to review sponsor-submitted proposals for concurrence and to address perceived data gaps in the assessments.

Conceptually, the data necessary for a preliminary carcinogenicity assessment could in some cases be limited to knowledge of the basic pharmacology of compounds found to interact with pathways or targets implicated in carcinogenesis (e.g., immunosuppressants, hormones, growth factor signaling pathways). Or, the assessment could be extensive in the case of compounds with new or poorly defined mechanisms of action. For the latter, additional studies may be needed to address concerns identified in completed studies or to fill perceived gaps in the data before prospectively deciding the value of conducting two-year rodent bioassays. Types of additional data could include (but may not be limited to) knowledge of drug class effects, toxicogenomic and cancer pathways analyses, available human data, expanded relevant endpoints in toxicology studies, and results from *in vitro* or short- or medium term *in vivo* models of tumor initiation/promotion.

Little or no evidence of a carcinogenic hazard, based on the preliminary assessment for a given compound, would provide sponsors the option to justify with a rationale for why conducting the two-year studies would not add value to the assessment of carcinogenic risk. For any pharmaceutical, the sponsor may also choose to conduct a two-year bioassay. The EWG must provide guidance on the scope of data necessary to justify omitting two-year bioassays, considering the endpoints discussed above.

Furthermore, when a preliminary assessment of a pharmaceutical provides clear or equivocal evidence of a carcinogenic hazard sponsors would need to justify a plan to address the risk. Such a plan may include a justification for not conducting the two-year rodent studies based on the strength of the identified risk. On the other hand, a sponsor may further characterize the predicted risk with additional investigational studies that could include two-year bioassays or alternative mouse models (rasH2, p53, etc.). The type of plan accepted would be informed by several considerations that will vary by drug; such additional considerations beyond those currently stated in S1A should be defined by the EWG in the revised guidance. Pivotal new considerations may include for example, the pharmacology of the compound, and/or the presence or absence of certain histopathologic changes in 6-month studies.

This staged weight-of-evidence approach takes into account our knowledge of pathways implicated in rodent and human carcinogenesis as well as the ‘negative’ predictivity demonstrated by databases compiled by PhRMA, FDA, and JPMA. It also allows for additional investigational studies in cases where existing data are considered insufficient to address concerns, and allows flexibility for incorporating new methodologies as they emerge. It is hoped that this proposal moves the assessment strategy toward a better prediction of carcinogenic risk to human subjects in addition to anticipating the outcome of 2-year rodent bioassays and the expected value or lack thereof from conducting them.

Issues to be Resolved

The following major issues have been defined by initial analyses of the data sets:

- Target and pathway related mechanistic/pharmacologic and understood secondary pharmacologic characteristics may contribute to the prediction of outcomes of carcinogenicity studies, and may improve prediction of potential human carcinogens. How this information will be used in a prospective way to define carcinogenicity testing strategies needs to be defined. Additional analyses confirming the value of this approach are needed.
- Off-target unexpected pharmacologic and toxicologic criteria such as histopathology from chronic toxicology studies, genetic toxicology testing and evidence of hormonal perturbations may also contribute to the prediction of outcomes of carcinogenicity studies. How these endpoints will be defined and how this information will be used in a prospective way to define carcinogenicity testing strategies also need to be explored.
- Which additional data may be needed to provide assurances of patient safety when waiving the need to conduct 2-year rodent carcinogenicity studies.
- Limited analyses of some of the data sets suggests that 2-year rat studies may provide new toxicological data unrelated to tumor findings that were not detected in 6-month chronic rat studies or chronic non-rodent studies. A thorough assessment of their relevance to human health is needed which may influence further testing strategies.
- Alignment would be needed on developing a process for reaching timely global decisions between sponsors and regulatory authorities in the course of drug development with regard to the carcinogenicity testing strategy.

Once defined, a prospective evaluation period of the proposed testing strategy will be needed.

Historical Background to the Proposal

Recent efforts (Reddy *et al*, 2010, *Vet Pathol* 47, 614-629) demonstrate good concordance between negative histopathology findings on a whole-animal basis from a chronic rat toxicology study, and negative outcome in a 2-year rat carcinogenicity study. These promising results triggered a PhRMA consortium to accumulate and critically analyze data from 182 compounds tested in chronic rat studies and 2-year rat carcinogenicity studies across 3 decades by 13 pharmaceutical companies, including the analyses of the results of genetic toxicology tests and evidence of on-target endocrine pharmacology and off-target hormonal perturbation in any toxicology study. Both successfully marketed pharmaceuticals as well as compounds discontinued from development were included (Sistare *et al*, 2011). In addition, the same assessment was applied to 86 IARC Human Carcinogens. The PhRMA database has been shared with FDA, EMA and MHLW. The JPMA and FDA have each conducted independent analyses of separate databases that include an additional 60 and 50 pharmaceuticals, respectively. The decision paradigm (NEG CARC) demonstrated potential to eliminate approximately 40% of rat 2-year testing across the historical data set without compromise to patient safety. Concerns were raised however that the proposed NEG CARC paradigm may allow an undefined percentage of pharmaceuticals with human relevant cancer risk to prospectively escape detection, that the empirical basis of NEG CARC as applied to the databases would be impractical in practice, and also that non-proliferative histopathologic changes of concern to humans may be missed if 2

years of testing in the rat are eliminated and reliance is placed on 6-month studies as the longest duration rat studies.

A critical and unblinded assessment of the PhRMA database was conducted by the EMA and shared confidentially with FDA and MHLW. The results from those critical analyses support the conclusion that understanding of target and biological pathway associated pharmacology and toxicology strengthens the overall value of the approach to stratifying human carcinogenic risk and assessing the added value of conducting a 2-year rat bioassay.

Establishing an Expert Working Group

The Expert Working Group (EWG) will consist of two members (nonclinical experts) nominated by the six parties of the ICH, and one member nominated by each of the ICH Observers. In addition, the following Interested Parties are invited to send a representative: Biotechnology Industry Organization (BIO). RHIs/ DRAs/DoH may also send one expert to this group.

Timeline

The request was submitted to the ICH Steering Committee (SC) in March 2012 and was approved by the SC thereby establishing a formal Expert Working Group, and allowed the EWG to meet face-to-face in June, 2012.

The EWG initiated further analyses of available data addressing the proposal, and agreed to focus on developing a modification to S1, but to first prepare a draft "Regulatory Notice for Public Input". This initial step is expected to be completed and to develop an aligned draft document at a face-to-face meeting of the EWG in November, 2012. Each regulatory health authority will then issue this draft "Regulatory Notice for Public Input" and solicit comments from the public to the proposal, the procedure, and the specific weight-of-evidence criteria. Comments received during 2013 will be reviewed by the S1 EWG with the goal of completing development of a final "Regulatory Notice for Public Input" that will specify the agreed upon details of the prospective trial data collection period. This final "Regulatory Notice" is planned to be published in June 2014 and will mark the beginning of the prospective data collection period. After collecting and incorporating results from the prospective analyses, a *Step 2* document is planned to be published in November, 2016, and a *Step 4* document finalized in November 2017.

