Proposed Change to Rodent Carcinogenicity Testing of Pharmaceuticals - Regulatory Notice for Public Input

Summary

A change to the current ICH S1 guidance on rodent carcinogenicity testing is being considered. The goal of this potential change is to introduce a more comprehensive and integrated approach to address the risk of human carcinogenicity of small molecule pharmaceuticals, and to define conditions under which 2-yr rodent carcinogenicity studies add value to that assessment.

Datasets evaluated by the ICH S1 expert working group (S1 EWG) suggest that knowledge of pharmacologic targets and pathways together with toxicological and other data can, in certain cases, provide sufficient information to anticipate the outcome of 2-yr rodent studies and their potential value in predicting the risk of human carcinogenicity of a given pharmaceutical. Consideration of this information is hypothesized to provide sufficient information to conclude that a given pharmaceutical in certain cases presents a negligible risk or, conversely, a likely risk of human carcinogenicity without conducting a 2-yr rodent study. It is envisioned that sponsors of such pharmaceuticals would provide Drug Regulatory Agencies (DRAs) a Carcinogenicity Assessment Document (CAD) which could justify a 'waiver request' that seeks to omit the conduct of 2-yr rodent studies. The CAD would address the overall carcinogenic risk of the investigational drug as predicted by the endpoints discussed in this document and a rationale for why the conduct of 2-yr rodent studies would or would not add value to that assessment.

Prospective evaluation of this proposed hypothesis is necessary to justify proceeding with revision of the ICH S1 guidance. A prospective evaluation period is sought wherein Sponsors will be requested to submit CADs to DRAs for all investigational pharmaceuticals with ongoing or planned 2-yr rodent studies. DRAs from each region will independently review the submitted assessments to evaluate the degree of concordance with Sponsors and between regulatory regions. During this prospective evaluation period the waiver requests are not to be granted and rather are intended solely for gathering experience and hypothesis testing. Submitted assessments will be compared to the outcome of the 2-yr rodent studies to evaluate the accuracy and relevance of the predictions to the actual experimental results. Experience from this prospective evaluation period is considered critical to informing the S1 EWG's efforts in revising the current paradigm of assessing the carcinogenicity of small molecules as described in ICH S1 guidance. Public comment is sought regarding the proposed change in approach to carcinogenicity assessment, on the prospective evaluation period intended to test this new approach, and on the weight-of-evidence (WOE) factors proposed for inclusion in CADs.

Introduction

Statement of the problem

The strategy of testing for carcinogenic potential was the first safety topic of ICH when this process started. The main topics were the need to conduct a study (S1A), the selection criteria for the rodent species (S1B) and the criteria for selection of the maximum dose (S1C). During the discussion in that period the relevance of the life-time carcinogenicity studies in rats and mice was already highly debated, but in the absence of an alternative the outcome of the negotiations did not really change the basic strategy of testing pharmaceuticals for human use in two rodent species. A proposal to delete the mouse as a second species did not receive sufficient support, although it paved the way to introduce transgenic mice with a 6-9 months treatment as an appropriate alternative (S1B).

In the following years considerable resources have been spent to evaluate the approaches using the transgenic mice (Cohen et al, 2001). Also other models and approaches received attention, especially the possibility to predict the outcome of carcinogenicity studies on the basis of the results of 3-months or 6-months studies (Cohen, 2004).

In this framework, researchers from a US-based company started a project with 60 company-owned and marketed compounds (Reddy et al, 2010) with the outcome that a negative histopathology result in rats (i.e. no evidence of hyperplasia in any organ) might be predictive for the absence of tumors in a 2-yr study. This led to the conduct of a much broader project involving 13 companies.

Historical Background

In 2011 a database analysis has been published by PhRMA (Sistare et al, 2011) confirming the conclusion of the earlier paper. Based on a dataset of 182 compounds it could be concluded that negative histopathology in a chronic rat study together with a negative result in genotoxicity and negative evidence of a hormonal mechanism would be useful in predicting a negative outcome of the carcinogenicity study for these compounds. This could apply to around 30-40% of the compounds.

In the discussion of these results with the DRAs, a question was raised regarding the impact of the pharmacological properties of the compounds, first for the false negative compounds, but with consequences for all compounds. The EU delegation has conducted an analysis and concluded that a majority of the tumor-inducing compounds, were found to induce these tumors in relation to its pharmacodynamic action. In addition some compounds associated with hepatocellular hypertrophy or liver enzyme induction were prone to induce tumors not only in liver, but also in thyroid and testes.

In addition to the PhRMA dataset, the FDA conducted a similar study with 50 unique compounds, and the JPMA conducted a study with 64 compounds unique from the PhRMA compound set. These datasets confirmed the earlier

analysis of the PhRMA dataset with respect to negative predictivity, as well as the EU analysis regarding the relation with the pharmacology. In the initial discussion on the relevance of rats and mice in the process coming to ICH S1B, both EU (van Oosterhout, et al 1997) and US (Contrera, et al 1997) have published a dataset of several hundreds of compounds with life-time carcinogenicity studies in rats and mice. The EU delegation has used the background data of the EU as well as the published data from FDA relating the pharmacology of the compounds and the outcome of the rat carcinogenicity studies. This analysis fully confirmed the conclusions reached earlier on the PhRMA database.

Conclusions from analyses conducted

From the analysis of the various datasets (PhRMA, FDA, JPMA, and EU + FDA) it can be concluded that based on pharmacology, genotoxicity, and chronic toxicity data (usually present at the end of phase 2 in the development of a new pharmaceutical) the outcome of the 2-yr rat carcinogenicity study can be predicted with reasonable assurance at the two extremes of the spectrum. Negative predictions can be made when predictive carcinogenic signals are absent and positive predictions can be made when such signals are present. In between a category of compounds still remain for which the outcome of the carcinogenicity studies cannot be predicted with sufficient certainty.

Proposal

The processes initiated by this proposal are expected to improve pharmaceutical carcinogenicity evaluations, reduce use of animals in accordance with the 3Rs (reduce/refine/replace) principles, reduce the use of other drug development resources, and reduce timelines to market authorization in some cases, all without compromise to patient safety. Analyses of the data sets described above, suggest that a carcinogenicity assessment could be completed for certain pharmaceuticals without conducting a 2-yr rat carcinogenicity study. From these databases it can be shown that pharmacologic and toxicologic data from numerous sources including toxicology studies of 6-months duration or shorter can be integrated to predict with sufficient certainty that a given pharmaceutical will fall into one of 3 main categories: Category 1 - so likely to be tumorigenic in humans that a product would be labeled as such and a 2-yr rat study would not add value; Category 2 - the available sets of pharmacologic and toxicologic data indicate that tumorigenic potential for humans is uncertain and a 2-yr rat study is likely to add value to human risk assessment. Category 3a – so likely to be tumorigenic in rats but not in humans through prior established and well recognized mechanisms known to be human irrelevant, that a 2-yr rat study would not add value; or Category 3b - so likely not to be tumorigenic in both rats or humans that no 2-yr rat study is needed.

A set of proposed WOE (Appendix 1) factors has been developed. During the prospective evaluation period sponsors are encouraged to apply the available WOE for each pharmaceutical prior to 2-yr rat study completion and to assign a pharmaceutical candidate to Category 1, 2, 3a or 3b in a CAD with respect to

the expected value and need for 2-yr rat carcinogenicity testing. Sponsors should submit the CAD to the DRAs explaining and justifying their position that a waiver decision is, or is not, appropriate for each pharmaceutical prior to knowing the outcome of carcinogenicity testing.

Scope and Process for a Prospective Evaluation Period

Objective

The intent of the prospective evaluation period is to gain experience and generate data that address critical aspects of proposed changes to ICH S1 guidance that could not be answered by retrospective analysis of the existing datasets. Specifically, these critical aspects include how well the WOE described herein will predict the outcome and value of 2-yr rat carcinogenicity study results, and how often the DRAs are in accordance with sponsors and with each other regarding the need to conduct a 2-yr rat study based on the arguments put forth in CADs.

Sponsors are requested to submit CADs for *all* investigational small molecule pharmaceuticals subject to a 2-yr rat carcinogenicity study under current ICH S1A Guideline as well as for those with ongoing rat carcinogenicity studies, provided that dosing has not exceeded 18 months duration. The date that the document was authored should be specified in the CAD in relation to the start of the study and state that the assessment was not influenced by any signal from the ongoing study. The results of the prospective evaluation period will inform future revisions to the ICH S1 guidances. CADs submitted under the prospective evaluation period are not considered regulatory documents or a substitute for the standard carcinogenicity assessment. This request is not applicable to investigational biologic pharmaceuticals that follow the ICH S6 and S6 Addendum guidance documents.

Content of Submitted CADs

Submissions should assess the carcinogenic potential for the investigational pharmaceutical under study, guided by the WOE approach described in Appendix 1. The CAD should address each factor considered pertinent to carcinogenic potential and not provide a general summary of the nonclinical profile of the pharmaceutical. Not all factors in Appendix 1 are expected to be applicable or available in all cases.

In addition to addressing the WOE in Appendix 1, the CAD should include the following critical elements:

1. Prediction of the actual tumor outcome from the planned/ongoing 2-yr rat study (positive/tumor target organs, or absence of tumors)
2. Projected value of the anticipated 2-yr rat outcome to the overall carcinogenicity assessment and human risk implications
3. Categorical assignment with explicit statement and explanation as to whether the CAD supports: 1) conducting the 2-yr rat study, or 2) a waiver request from conducting the 2-yr study

Evaluation of CADs
The intent of the prospective evaluation period is to generate data relevant to future changes to ICH S1 guidance. As such, submitted CADs will have no impact on the drug development program in any region. Actual waivers of the 2-yr rat study will not be granted, nor will CADs be used to support regulatory actions on development programs.

Each DRA will independently review submitted CADs at the time of receipt for the adequacy of the prediction and will only provide feedback to sponsors when the assessments inadequately address the 3 critical elements cited above. DRAs will convene to assess the concordance in predictions between DRAs and sponsors and among DRAs.

CADs will again be evaluated according to each of the following 3 points after receiving results of the corresponding 2-yr rat study. The CADs will be evaluated based on the following attributes:

1. Accuracy of the prediction compared to the 2-yr rat tumor outcome using the WOE described herein
2. Accuracy of the sponsor's and the DRAs' original categorical assignments relative to actual overall study outcome.
3. Regulatory impact when the predicted tumor outcome may differ from the actual tumor outcome.

The DRA's will maintain product confidentiality in conducting independent analyses of the above attributes as well as of the type of compounds. Summary of anonymized results and the extent of sponsor participation will be periodically reviewed by the ICH S1 EWG. Concordance in interpretations between DRAs and sponsors and among the DRAs will be analyzed at study termination. Final results of the prospective evaluation period will be reviewed by the S1 EWG to inform revision of the current ICH S1 guidance. Publication in a peer-reviewed toxicological journal is planned.

The prospective evaluation period will end after approximately fifty CADs are received by the DRAs. The goal of fifty CADs may change depending on the diversity of compounds addressed and the number of pharmaceutical companies that participate. For example, a narrow focus on few drug classes and/or participation by few pharmaceutical companies may introduce bias into the study and necessitate an increase in the number of CADs. Based on analysis of the number of rat study protocols and final rat study reports received by the US FDA since 2010, it is estimated that a two-year data collection period will be needed to reach the goal of fifty CADs. Success of this effort hinges on the active participation by pharmaceutical companies in submitting CADs to DRAs for review.

Process of Submitting CADs
Sponsors are requested to submit CADs to the US FDA, EU EMA, and Japanese MHLW at the addresses below. We request that CADs be sent to all three DRAs whether or not development programs are established in each region. CADs are requested for *all* investigational small molecule

pharmaceuticals subject to a 2-yr rat carcinogenicity study under current ICH S1 guidance as well as for those with ongoing rat carcinogenicity studies, provided that dosing has not exceeded 18 months duration. The final results of the 2-yr rat study are encouraged to be submitted when available, irrespective of the timing of the marketing application.

Public Comments Requested

Please submit comments regarding the proposed change in approach to carcinogenicity assessment, on the prospective evaluation period intended to test this new approach, and on the WOE factors proposed for inclusion in carcinogenicity assessment documents to:
ADDRESSES HERE
EMA , FDA, MHLW,

References

Cohen SM (2004) Human Carcinogenic Risk Evaluation: An Alternative Approach to the Two-Year Rodent Bioassay. Toxicol Sci. 80, 225–229

Cohen SM, Robinson D, MacDonald J. (2001)Alternative Models for Carcinogenicity Testing. Toxicol. Sci 64, 14–19

Contrera JF, Jacobs AC, DeGeorge JJ (1997) Carcinogenicity Testing and the Evaluation of Regulatory Requirements for Pharmaceuticals. Regulatory Toxicology and Pharmacology 25, 130-145

Cook JC, Klienefelter GR, Hardisty JF, Sharpe RM, Foster PMD. (1999) Rodent Leydig cell tumorigenesis: a review of the physiology, pathology, mechanisms and relevance to humans. Crit. Rev. Toxicol. 29, 169-261.

McClain RM. (1989). The significance of hepatic microsomal enzyme induction and altered thyroid function in rats: implications for thyroid gland neoplasia. Toxicol Pathol 17, 294-306.

Reddy MV, Sistare FD, Christensen JS, DeLuca JG, Wollenberg GK, DeGeorge JJ. (2010) An Evaluation of Chronic 6- and 12-Month Rat Toxicology Studies as Predictors of 2-Year Tumor Outcome. Vet Pathol 47:614 – 629

Sistare FD, Morton D, Alden C, Christensen J, Keller D, De Jonghe S, Storer RD, Reddy MV, Kraynak A, Trela B, Bienvenu J, Bjurström S, Bosmans V, Brewster D, Colman K, Dominick M, Evans J, Hailey JR, Kinter L, Liu M, Mahrt C, Marien D, Myer J, Perry R, Potenta D, Roth A, Sherratt P, Singer T, Slim R, Soper K, Fransson-Steen R, Stoltz J, Turner O, Turnquist S, van Heerden M, Woicke J, DeGeorge JJ. (2011) An Analysis of Pharmaceutical Experience with Decades of Rat Carcinogenicity Testing: Support for a Proposal to Modify Current Regulatory Guidelines. Toxicologic Pathology 39, 716-744

Van Oosterhout JPJ, Van der Laan JW, De Waal EJ, Olejniczak K, Hilgenfeld M, Schmidt V, Bass R (1997). The utility of Two Rodent species in Carcinogenic Risk Assessment of Pharmaceuticals in Europe. Regulatory Toxicology and Pharmacology 25, 6-17

Appendix 1. Weight-of-Evidence Factors for Consideration in a Carcinogenicity Assessment Document

Each of the factors listed below should be considered in formulating a prediction in the outcome and value of conducting a 2-yr rat carcinogenicity study and an overall integrated assessment of the carcinogenic risk for humans. Some factors can be appropriate for both, others more appropriate for one or the other purpose.

- **Knowledge of intended drug target and pathway pharmacology, secondary and off-target pharmacology, & drug target distribution in rats and humans.**
  Target and pathway related mechanistic/pharmacologic and understood secondary pharmacologic characteristics can contribute to the prediction of outcomes of carcinogenicity studies, and can improve prediction of potential human carcinogens. The CAD is expected to convey a thorough and critical assessment of the sponsor's knowledge of all such characteristics including a comprehensive literature review specifically addressing carcinogenicity risk. Examples of such data sources include the following:
  - Prior experience with other molecules in the drug class
  - Experience with human genetic polymorphisms in the target or pathway
  - Clinical trial data
  - Genetically engineered rodent models
  - Unintended pharmacology
  - Hormonal perturbation
  - Targeted tissue genomic biomarker measurements

- **Genetic Toxicology Study Results**
  The criteria in ICH S2 [R1] will be used to evaluate genetic toxicology data using a weight-of-evidence approach.

- **Histopathologic Evaluation of Repeated Dose Rat Toxicology Studies**
  Histopathologic risk factors of neoplasia should be evaluated in the 6-month chronic rat study. Findings seen only in shorter term repeated dose rat toxicity studies are generally considered of less value for 2-yr rat study outcome prediction, but should be addressed. Histopathologic findings of particular interest include cellular hypertrophy, diffuse and/or focal cellular hyperplasia, persistent tissue injury and/or chronic inflammation, preneoplastic changes, and tumors. It is important to note that liver tumors are observed at relatively high frequency in the rat, sometimes with Leydig cell and thyroid follicular cell tumors. Hepatocellular hypertrophy associated with increased liver weight often results from hepatic enzyme induction, the latter being a well understood mechanism of rodent specific tumorigenesis at these sites with little relevance to humans (McClain, 1989; Cook et al., 1999).

- **Exposure Margins in Chronic Rat Toxicology Studies**
  A high exposure margin in a chronic rat toxicology study absent of any carcinogenic risk factors can provide additional support for a carcinogenicity study waiver. The inability to achieve high exposure margins in a chronic rat

toxicology study due to limitations of tolerability, pharmacology, or absorption, would not preclude a carcinogenicity study waiver.

- **Evidence of Hormonal Perturbation**
  Evidence of hormonal perturbation should be considered from both repeated-dose and reproductive toxicology studies. Such evidence can come from weight, gross and/or microscopic changes in endocrine organs or parameters from reproductive toxicology studies. Serum hormone levels can be useful to address findings but are not always essential.

- **Immune Suppression**
  Immunosuppression can be a causative factor for tumorigenesis in humans. As such, immunotoxicological parameters should be examined according to the ICH S8 guideline.

- **Special Studies and Endpoints**
  Data from special stains, new biomarkers, emerging technologies, and alternative test systems can be submitted with scientific rationale to help explain or predict animal and/or human carcinogenic pathways and mechanisms when they would contribute meaningfully.

- **Results of Non-Rodent Chronic Study**
  Assessment of carcinogenic risk factors in the non-rodent toxicology studies should be considered for human risk assessment regardless of results in the chronic rat study.

- **Transgenic Mouse Study**
  A transgenic mouse carcinogenicity study (usually rasH2 or p53+/- mouse) is not required for the WOE argument. However, if conducted on a case-by-case basis, a transgenic mouse carcinogenicity study can contribute to the WOE. .