Publicly available submissions may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

Dated: February 28, 2013.

Melinda K. Plaisier,

Acting Associate Commissioner for Regulatory Affairs, Office of Regulatory Affairs.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2013–N–0222]

International Conference on Harmonisation; Proposed Change to Rodent Carcinogenicity Testing of Pharmaceuticals; Request for Comments

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice; request for comments.

SUMMARY: The Food and Drug Administration (FDA or the Agency) is considering a proposed change to the International Conference on Harmonisation (ICH) Sl guidance on rodent carcinogenicity testing. 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-year rodent carcinogenicity studies add value to that assessment. The basis of this proposed change is the retrospective analyses of several datasets that reflect three decades of experience with such studies. The datasets suggest that knowledge of certain pharmacologic and toxicologic data can sometimes provide sufficient information to anticipate the outcome of 2-year rodent studies and their potential value in predicting the risk of human carcinogenicity of a given pharmaceutical. FDA is requesting public comment regarding a proposed change in approach to carcinogenicity assessment, on the prospective evaluation period intended to test this new approach, and on the proposed weight-of-evidence factors for carcinogenicity assessment.

DATES: Submit electronic or written comments on the proposed change by May 17, 2013.

ADDRESSES: Submit electronic comments on the proposed change to *http://www.regulations.gov.* Submit written comments to the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Todd Bourcier, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 22, rm. 3102, Silver Spring, MD 20993–0002, 301–796–1179.

SUPPLEMENTARY INFORMATION:

I. Background

FDA is considering a change in the current ICH S1 guidance on rodent carcinogenicity testing.[1] 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-year 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-year rodent studies and their potential value in predicting the risk of human carcinogenicity of a given pharmaceutical. It is hypothesized that consideration of this information can 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-year rodent study. It is envisioned that sponsors of such pharmaceuticals would provide drug regulatory agencies (DRAs) a carcinogenicity assessment document (CAD) that could justify a ''waiver request'' that would seek to omit the conduct of 2-year 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-year 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 would be sought wherein sponsors would be requested to submit CADs to DRAs for all investigational pharmaceuticals with ongoing or planned 2-year rodent studies. DRAs from each region would 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 would not to be granted and rather are intended solely for gathering experience and hypothesis testing. Submitted assessments would be compared to the outcome of the 2-year 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 the ICH S1 guidance. FDA is requesting public comment 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.

II. Past Experience With Carcinogenicity Assessment

The strategy of testing for carcinogenic potential was the first safety topic addressed by ICH. The main topics were the need to conduct a study (ICH S1A), the selection criteria for the rodent species (ICH S1B), and the criteria for selecting the maximum dose (ICH S1C). During the discussion in that period, the relevance of the lifetime 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 not use the mouse as a second species did not receive sufficient support, although it paved the way to introduce transgenic mice with a 6- to 9-month treatment as an appropriate alternative (ICH S1B).

In the following years, considerable resources have been spent to evaluate the approaches using the transgenic mice (Ref. 1). 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- to 6-month studies (Ref. 2).

[1] See the ICH S1 guidance documents, ''S1A The Need for Long-Term Rodent Carcinogenicity Studies of Pharmaceuticals'' (ICH S1A), ''S1B Testing for Carcinogenicity of Pharmaceuticals'' (ICH S1B), and ''S1C(R2) Dose Selection for Carcinogenicity Studies of Pharmaceuticals'' (ICH S1C), available on the Internet at *http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm or http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.*

In this framework, researchers from a U.S.-based company started a project with 60 company-owned and marketed compounds (Ref. 3) 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-year study. This led to the conduct of a much broader project involving 13 companies.

A. Carcinogenicity Studies

In 2011, PhRMA published a database analysis (Ref. 4) confirming the conclusion of an 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 conclusion could apply to around 30 percent to 40 percent 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 European Union (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 their 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, FDA conducted a similar study with 50 unique compounds, and the Japanese Pharmaceutical Manufacturers' Association (JPMA) conducted a study with 64 unique compounds 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. From discussions held in formulating ICH S1B guidance, both the European Union (Ref. 5) and the United States (Ref. 6) published a dataset of several hundreds of compounds with lifetime carcinogenicity studies in rats and mice. The EU delegation has used the background data of the European Union, 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.

B. 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-year 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. An in-between category of compounds still remains for which the outcome of the carcinogenicity studies cannot be predicted with sufficient certainty.

III. Proposal

The processes initiated by this prospective proposal are expected to improve pharmaceutical carcinogenicity evaluations, reduce use of animals in accordance with the 3Rs (reduce/refine/replace) principle, 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 datasets described in section II suggest that a carcinogenicity assessment could be completed for certain pharmaceuticals without conducting a 2-year rat carcinogenicity study. From these databases, it can be shown that pharmacologic and toxicologic data from numerous sources, including toxicology studies of 6-month duration or shorter, can be integrated to predict with sufficient certainty that a given pharmaceutical will fall into one of three main categories:

- Category 1—so likely to be tumorigenic in humans that a product would be labeled as such, and a 2-year 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-year rat study is likely to add value to human risk assessment; and
- 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-year rat study would not add value; or
- Category 3b—so likely not to be tumorigenic in either rats or humans that no 2-year rat study is needed.

A set of proposed WOE (see Appendix 1 of this document) factors has been developed. During the prospective evaluation period sponsors would be encouraged to apply the available WOE for each pharmaceutical prior to 2-year 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-year rat carcinogenicity testing. Sponsors would submit the CAD to the DRAs explaining and justifying their position that a waiver decision is, or is not, appropriate for each pharmaceutical before knowing the outcome of carcinogenicity testing.

IV. Scope and Process for a Prospective Evaluation Period

A. Objective

The intent of the prospective evaluation period is to gain experience and generate data that would address critical aspects of proposed changes to the ICH S1 guidance that could not be answered by retrospective analysis of the existing datasets. Specifically, these critical aspects include how well the WOE will predict the outcome and value of 2-year 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-year rat study based on the arguments put forth in CADs.

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

[2] See the ICH guidance documents, ''S6 Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals'' and ''S6 Addendum to Preclinical Safety Evaluation on Biotechnology-Derived Pharmaceuticals,'' available at *http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm* or *http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.*

B. Content of Submitted CADs

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

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

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

C. Evaluation of CADs

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

Each DRA would independently review submitted CADs at the time of receipt for the adequacy of the prediction and would only provide feedback to sponsors when the assessments inadequately address the three critical elements cited in section IV.B of this document. DRAs would convene to assess the concordance in predictions between DRAs and sponsors and among DRAs.

The CADs would again be evaluated, based on the following three points, after the DRAs have received results of the corresponding 2-year rat study:

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

The DRAs would maintain product confidentiality in conducting independent analyses of the attributes data, as well as of the type of compounds. Summary of anonymized results and the extent of sponsor participation would be periodically reviewed by the ICH S1 EWG. Concordance in interpretations between DRAs and sponsors and among the DRAs would be analyzed at study termination. Final results of the prospective evaluation period would 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 would end after approximately 50 CADs have been received by the DRAs. The goal of 50 CADs could change, depending on the diversity of compounds addressed and the number of pharmaceutical companies that would participate. For example, a narrow focus on few drug classes and/or participation by few pharmaceutical companies could 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 FDA since 2010, it is estimated that a 2-year data collection period would be needed to reach the goal of 50 CADs. Success of this effort hinges on the active participation by pharmaceutical companies in submitting CADs to DRAs for review.

D. Process of Submitting CADs

Sponsors would be requested to submit CADs to FDA; the EU European Medicines Agency; and the Japanese Ministry of Health, Labour and Welfare. We would request that CADs be sent to all three DRAs, whether or not development programs are established in each region. CADs would be requested for *all* investigational small molecule pharmaceuticals subject to 2-year rat carcinogenicity study under the current ICH S1 guidance, as well as for those with ongoing rat carcinogenicity studies, provided that dosing has not exceeded the 18-month duration. We would encourage that the final results of the 2-year rat study be submitted when available, irrespective of the timing of the marketing application.

V. Comments

Interested persons may 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. Submit either electronic comments regarding this document to *http://www.regulations.gov* or written comments to the Division of Dockets Management (see **ADDRESSES**). It is only necessary to send one set of comments. Identify comments with the docket number found in brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management (see **ADDRESSES**) between 9 a.m. and 4 p.m., Monday through Friday, and will be posted to the docket at *http://www.regulations.gov*.

VI. References

The following references have been placed on display in the Division of Dockets Management (see **ADDRESSES**) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday, and are available electronically at *http://www.regulations.gov*.

1. Cohen, S.M., D. Robinson, and J. MacDonald, ''Alternative Models for Carcinogenicity Testing'', *Toxicological Sciences,* vol. 64, pp. 14–19, 2001.
2. Cohen, S.M., ''Human Carcinogenic Risk Evaluation: An Alternative Approach to the Two-Year Rodent Bioassay'', *Toxicological Sciences,* vol. 80, pp. 225–229, 2004.
3. Reddy, M.V., F.D. Sistare, J.S. Christensen, et al., ''An Evaluation of Chronic 6- and 12-Month Rat Toxicology Studies as Predictors of 2-Year Tumor Outcome'', *Veterinary Pathology,* vol. 47, pp. 614–629, 2010.
4. Sistare, F.D., D. Morton, C. Alden, et al., ''An Analysis of Pharmaceutical Experience With Decades of Rat Carcinogenicity Testing: Support for a Proposal to Modify Current Regulatory Guidelines'', *Toxicologic Pathology,* vol. 39, pp. 716–744, 2011.
5. Van Oosterhout, J.P.J., J.W. Van der Laan, E.J. De Waal, et al., ''The Utility of Two Rodent Species in Carcinogenic Risk Assessment of Pharmaceuticals in Europe'', *Regulatory Toxicology and Pharmacology,* vol. 25, pp. 6–17, 1997.
6. Contrera, J.F., A.C. Jacobs, and J.J. DeGeorge, ''Carcinogenicity Testing and the Evaluation of Regulatory Requirements for Pharmaceuticals'', *Regulatory Toxicology and Pharmacology,* vol. 25, pp. 130–145, 1997.

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

Each of the following factors should be considered in formulating a prediction in the outcome and value of conducting a 2-year 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, and 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)[3] 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-year 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 (Refs. 1 and 2).

• *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 because of 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 guidance.[4]

• *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.

References

The following references have been placed on display in the Division of Dockets Management (see **ADDRESSES**) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday, and are available electronically at *http://www.regulations.gov.*

1. Cook, J.C., G.R. Klinefelter, J.F. Hardisty, et al., ''Rodent Leydig Cell Tumorigenesis: A Review of the Physiology, Pathology, Mechanisms and Relevance to Humans'', *Critical Reviews in Toxicology,* vol. 29, pp. 169–261, 1999.
2. McClain, R.M., ''The Significance of Hepatic Microsomal Enzyme Induction and Altered Thyroid Function in Rats: Implications for Thyroid Gland Neoplasia'', *Toxicologic Pathology,* vol. 17, pp. 294–306, 1989.

Dated: March 12, 2013.

Leslie Kux,

Assistant Commissioner for Policy.

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[3] See the ICH guidance ''S2(R1) Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use,'' available at *http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm* or *http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.*

[4] See the ICH guidance ''S8 Immunotoxicity Studies for Human Pharmaceuticals,'' available at *http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm* or *http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.*

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2013–N–0001]

General and Plastic Surgery Devices Panel of the Medical Devices Advisory Committee; Notice of Meeting

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

This notice announces a forthcoming meeting of a public advisory committee of the Food and Drug Administration (FDA). The meeting will be open to the public.

Name of Committee: General and Plastic Surgery Devices Panel of the Medical Devices Advisory Committee.

General Function of the Committee: To provide advice and recommendations to the Agency on FDA's regulatory issues.

Date and Time: The meeting will be held on May 2, 2013, from 8 a.m. to 6 p.m.

Location: Hilton Washington DC North/Gaithersburg, Salons A, B, C and D, 620 Perry Pkwy., Gaithersburg, MD 20877. The hotel's telephone number is 301–977–8900.

Contact Person: Jamie Waterhouse, Center for Devices and Radiological Health, Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD 20993, or FDA Advisory Committee Information Line, 1–800–741–8138 (301–443–0572 in the Washington, DC area). A notice in the **Federal Register** about last minute modifications that impact a previously announced advisory committee meeting cannot always be published quickly