Business Plan

S1: Rodent Carcinogenicity Studies for Human Pharmaceuticals

Dated and endorsed by the Steering Committee on 14 November 2012

Introduction

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 expected to clarify and update the criteria for deciding whether the conduct of a 2-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.

1. The issue and its costs

- *What problem/issue is the proposal expected to tackle?*

The proposed change to the current S1 harmonized guideline is expected to improve the testing strategy for assessing the human risk of pharmaceuticals while reducing the frequency for conducting 2-year rat carcinogenicity studies. A sufficiently robust testing strategy that would enable omission of 2-year rat studies will require supportive data and a prospective assessment of proposed criteria, in order to justify adoption.

- *What are the costs (social/health and financial) to our stakeholders associated with the current situation or associated with "non action"?*

A published proposed decision paradigm suggested by PhRMA indicates that the outcome of past positive 2-year rat carcinogenicity studies with pharmaceutical candidates could be predicted with 80% accuracy from information available from shorter term studies. Additional analyses of these and other data support the notion that known target-related and secondary pharmacology can provide additional insight and might further improve the prediction of human carcinogenicity of pharmaceuticals. These analyses suggest that the number of 2-year rat studies could be reduced under certain conditions by approximately 40% or more, without significant risk to the public health. Conducting unnecessary 2-year rat testing: (1) uses ~600 animals for each 2-year rat carcinogenicity study conducted; (2) adds 2 to 3 years for completion of nonclinical

studies supporting registration, and in so doing can prolong the regulatory process and can delay patient access to those new medications; (3) expends industry resources to plan, conduct, analyze, and report (and also Regulatory Authority resources to review) - up to an estimated $3.75 M in costs for all efforts associated with the completion and evaluation of each unnecessary 2-year rat carcinogenicity study.

2. Planning

- *What are the main deliverables?*

A Step 4 change to ICH S1 Guidance: The results from the PhRMA data survey on 182 pharmaceuticals and 86 additional IARC chemicals classified as likely human carcinogens have been published. The PhRMA database has been shared with regulatory authorities. Additional databases have been generated by JPMA and FDA and analyses conducted by EMA and all have been shared, and more publications are expected.

- *What resources (financial and human) would be required?*

  (1) Constitution and active/dedicated participation by industry, regulatory, and ad hoc advisory members of the expert working group,

  (2) PhRMA, EFPIA and JPMA companies dedicated staff to mine existing data and have exhausted all sources of data available to them prior to 2008. However, FDA, PMDA and EMA may wish to mine independent datasets not available to PhRMA, EFPIA and JPMA companies from smaller non-member pharmaceutical companies or from the approximately 50 compounds for which carcinogenicity data has been generated since 2008. It is unclear whether regulatory authorities will be able to gather the human resources needed for such an additional effort and what impact on timing this may have. Agreement has been reached to design into the overall strategy a prospective assessment to "practice" this approach over an approximate 2-yr trial period, which involves sponsors submitting a non-binding waiver request based on meeting EWG-proposed criteria.

- *What are the time-frame and key milestones of the project?*

In order to proceed to an ICH Step 2 document it will be necessary to first prepare a draft "Regulatory Notice for Public Input". This initial step is expected to be completed in November 2012. Each regulatory health authority will then issue this draft "Regulatory Notice for Public Input" and solicit comments from their public regions to the proposal. Using the comments received, a final “Regulatory Notice” is expected to be published by June 2014; publication of this document will mark the beginning of a prospective data-

gathering period which is necessary prior to proceeding to *Step 2*. After collecting and incorporating the prospective experience gained, a *Step 2* document is planned to be published in November 2016 and a *Step 4* document finalized in November 2017.

3. The impacts of the project

- *What are the likely benefits (social, health and financial) to our key stakeholders of the fulfillment of the objective?*

The analyses of several published databases suggest that certain test criteria together with knowledge of drug primary and secondary pharmacologic actions can be used to correctly predict rat carcinogenicity outcome with good sensitivity. Improving the testing strategy is expected to reduce the number of 2-year rodent studies conducted in assessing the carcinogenic potential of human pharmaceuticals. Approximately 600 fewer animals would be spared for each 2-year rat carcinogenicity study avoided. An additional 400 fewer animals would be used for each pharmaceutical if the approach and timeline considerations encourage expanded use of an alternative mouse model of carcinogenicity in place of the conventional 2-year mouse study. The timeline for completion of nonclinical studies supporting registration potentially could be shortened by 2 to 3 years and registration timelines could be accelerated depending on the clinical program timeline. Both industry and regulatory resources applied in support of product development and review may be reduced, including up to an estimated $3.75 M reduction in costs for all efforts associated with the completion and evaluation of each 2-year rat carcinogenicity study. The potential to eliminate much of the uncertainty around carcinogenic risk earlier in development would be significant and could improve portfolio management.

- *What are the regulatory implications of the proposed work – is the topic feasible (implementable) from a regulatory standpoint?*

The regulatory implications are on the one hand, resource savings from not having to review and assess 2-year rat carcinogenicity studies for compounds that would have little or no impact on regulatory decision-making. On the other hand, regulatory authorities will need to agree globally on a new process and clear criteria that involve an assessment of the adequacy and the interpretation of such shorter term test results for exempting the conduct of a 2-year rat carcinogenicity study. This would increase the regulatory review time dedicated to assessing waiver requests, and in developing guidelines for communicating risk in drug labels in cases where 2-year rat studies have been waived. An overall effect on regulatory resources cannot be established yet.

Regulatory authorities may further need assurances that no human relevant chronic study findings should be seen in the rat beyond 6-months of dosing since this would be the longest rat study duration to support marketing if the proposal is adopted. Furthermore a revision to ICH S1 may need to specify that ICH M3 and S4 Q&A's may need to be addressed if this issue is deemed to be of significance.

4. Post-hoc evaluation

- *How and when will the results of the work be evaluated?*

Not applicable.