A Pharmaceutical Regulator’s View on the Utility of Adverse Outcome Pathways for Carcinogenicity Assessment

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Tina the Delegate

In simple terms, tell me about toxicology so I can understand it.

One Hour Later

And that’s how it all... uh-oh.

If I am reading your body language correctly, you’re saying I could have shortened that.
An adverse outcome pathway (AOP) is a model that identifies the sequence of molecular and cellular events required to produce a toxic effect when an organism is exposed to a substance. Construction of an AOP can:

- Organise information about biological interactions and toxicity mechanisms into models that describe how exposure to a substance might cause illness or injury.
- Suggest cell- or biochemical-based tests for pathway elements that could be used to develop testing strategies for targeted toxicity.
- Identify steps in a toxicity mechanism that need improved characterisation.
AOPs are made up of specific elements:

A **molecular initiating event** is an interaction between the toxic substance and an organism. This interaction begins the toxicity process.

**Key events** after the molecular initiating event characterise the progression of the toxicity. Early key events can include changes in protein production or molecular signalling that occur in individual cells. Later key events can include altered tissue or organ function.

**Adverse outcomes** may occur at individual or population levels. An adverse outcome for an individual organism can include disease, impaired development, or impaired reproduction. Population adverse outcomes can include changes in population structure or local extinction of a species.
There is increasing interest in approaches that gather toxicity data. Because toxic effects cannot be predicted by any one test, it is important to test a substance using a number of tests, and then to evaluate the combined data to predict potential toxic effects.

AOPs are key to combining the data generated by this approach.
Rodent Carcinogenicity Studies for Human Pharmaceuticals

The ICH Guideline on the need for carcinogenicity studies of pharmaceuticals was finalised in 1995.

The basic scheme comprises one long-term rodent carcinogenicity study, plus one other study of the type that supplements the long-term carcinogenicity study and provides additional information that is not readily available from the long-term assay.

These may include models of initiation-promotion in rodents or models of carcinogenesis using transgenic or neonatal rodents.

However, there are too many “false positives” in the rodent studies that do not predict a concern for humans.
It has been long considered that predicting the outcome of life-time carcinogenicity studies in rats is possible in some instances. (see van der Laan JW, Jones D R et al. Crit Rev Toxicol. 2016 Aug;46(7): 587-614).

We conducted an analysis of a dataset based on the pharmacology of 255 compounds from industrial and regulatory sources.

It was proposed that knowledge of the intended drug target and pathway pharmacology should enhance the prediction of either positive or negative outcomes of rat carcinogenicity studies.
The goal of this analysis was to review the pharmacological properties of compounds together with the histopathology findings from the chronic toxicity study in rodents in order to introduce an integrated approach to estimate the risk of human carcinogenicity of pharmaceuticals.

It was believed that this approach would allow scientists to define conditions under which 2-year rat carcinogenicity studies will or will not add value to such an assessment.

The work demonstrated the possibility of a “regulatory waiver” for a carcinogenicity study in rats by applying the proposed prediction approach in a number of case studies.
The ICH Steering Committee did endorse a change to the current S1 Harmonised Guidelines on rodent carcinogenicity testing to introduce a more comprehensive and integrated approach to addressing the risk of human carcinogenicity of pharmaceuticals, 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.
Hypothesis: the knowledge of pharmacological targets and pathways, together with toxicological and other data, of a given pharmaceutical can provide sufficient information to conclude that it presents a negligible risk or a likely risk of human carcinogenicity **without conducting a 2-year rat carcinogenicity study**, *i.e.* essentially an **Adverse Outcome Pathway** approach.

This should lead to a reduction in animals used (3Rs), saving costs, accelerate development process.
The ICH Expert Working Group proposed a prospective evaluation period (PEP) approach:

**Carcinogenicity Assessment Document (CAD):**

- Address the overall carcinogenic risk of an investigational drug based on weight of evidence (WOE) factors
- Assign the drug candidate to Category 1, 2, 3A or 3B with respect to the expected value
- Provide a rationale for why the conduct of 2-year rat carcinogenicity studies would or would not add value to that assessment
## Proposed Classifications

<table>
<thead>
<tr>
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<th>Likely to be tumorigenic in humans. Product would be labelled as such and life-time rat, and/or mouse, or alternative transgenic mouse carcinogenicity studies would not add value.</th>
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<tbody>
<tr>
<td>2</td>
<td>The available sets of pharmacology and toxicology data indicate that tumorigenic potential for humans is uncertain and rodent carcinogenicity studies are likely to add value to human risk assessment</td>
</tr>
<tr>
<td>3a</td>
<td>Likely to be tumorigenic in rats, <strong>but not in humans</strong> through <strong>prior established and well recognised mechanisms</strong> known to be human irrelevant, that a 2-year rat study would not add value</td>
</tr>
<tr>
<td>3b</td>
<td>Likely not to be tumorigenic in both rats or humans, so that no 2-year rat study is needed</td>
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Experts from Drug Regulatory Agencies (DRAs) from each region, *i.e.* USA, Europe (including Swiss Medic) Japan, Canada, independently review the submitted assessments to evaluate the degree of concordance with sponsors and between regulatory regions.

During this prospective evaluation period waiver requests will not be granted in practice. The data are collected solely for real world experience.

Submitted CADs will subsequently be compared to the outcome of the 2-year rat carcinogenicity studies, assessed by other experts “blinded” to the CAD decision, to evaluate the accuracy of the predictions to the actual experimental results.
The data being evaluated are:

**Pharmacology** - Knowledge of intended drug target and pathway pharmacology, secondary pharmacology, and drug target distribution in rats and humans

**Genetic Toxicology** Study Results

**Histopathological Evaluation** of Repeated Dose Rat Toxicology Studies

**Metabolic Profile**

Any Evidence of **Hormonal Perturbation**

**Immune Suppression**

**Special Studies and Endpoints** (special stains, new biomarkers, emerging technologies, and alternative test systems)

**Results of Non-Rodent Chronic Study**
The acceptance period for CAD submissions closed on 31 December 2017. A total of 48 CADs submitted by 22 sponsors were reviewed and categorised by DRAs.

The DRAs have now received and reviewed the majority of Final Summary reports (FSRs) from completed 2 year rat carcinogenicity studies. There have been a number of cases where it was unanimously agreed that the existing weight of evidence was sufficiently informative of human carcinogenic risk that a 2-year bioassay would not add substantial value to the assessment.
A “Step 1” Guideline is anticipated in November 2020. The final guideline is scheduled for May, 2022.

The main divergences between the EU and other regulatory authorities are related to the overall strategy for the weight of evidence approach and the necessity of a mouse study.

“To be different or to follow another way of thinking, does not mean that somebody’s heart is in the wrong place”
Proposal 1
Default regulatory approach is for Sponsors to conduct WOE Carcinogenicity assessment at end of Phase II (EOP2), or earlier – Favoured by EU.

Proposal 2
Default regulatory approach is for Sponsors to plan to conduct a 2 year rat study per current S1B guidance. Under certain scenarios defined by guiding criteria, a Sponsor may conduct a WOE assessment as an alternative to the ‘default’ regulatory approach, to be submitted at EOP2 or earlier. – Favoured by other DRAs

Based on Sponsor’s WOE, DRA decides whether 1) there is sufficient evidence to reach a conclusion on carcinogenic potential or if additional studies other than a rat bioassay are needed or 2) conducting the 2 year rat bioassay will have added value in establishing carcinogenic potential (i.e., unanswered questions can only be addressed by conducting a 2 year rat bioassay).
Need for Mouse Study

Proposal 1
If a WOE is an acceptable alternative to the rat bioassay, there is no expectation that a mouse study would be conducted. – Favoured by EU.

Proposal 2
A mouse study (Tg or 2yr) would still be conducted in most cases regardless of the decision on the rat study. - Favoured by USA, Japan et al.
The way forward isn’t going to be easy, but the end result should be worth while!
Regulatory Guidelines
Regulatory guidelines are like the modern map of the London Underground.

They don’t completely represent the “real” world.

There’s almost always more than one way to reach an objective and the recommended route might not be the one you should follow!
Samuel Johnson said “Patriotism is the last refuge of the scoundrel.”

I say “Rigorously following Regulatory Guidelines is the last refuge of those who don’t know how to develop medicines!!.”

NEVER FOLLOW A REGULATORY GUIDELINE IF THERE IS A GOOD SCIENTIFIC RATIONALE NOT TO!!!
Problem Areas and How to Resolve Them
Scientific Advice!!
Risk comes from not knowing what you’re doing, Warren Buffett

That’s not what I expected when I asked for advice!
The MHRA have provided scientific and regulatory advice to sponsors for many years.

Scientific advice can be requested during any stage of the initial development of the medicinal product (before submission of a marketing authorisation application), and also during the pre-submission period for a variation to an existing marketing authorisation.
The MHRA Licensing Division held about 250 Scientific Advice meetings with Companies in 2019.

The MHRA Clinical Trials Unit has had over 100 meetings with companies, academic institutes or hospital groups over the last 8 months (many, many related to COVID-19!!)

The CTU’s email helpline fields about 250 queries a month.