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COMMENTARY

EMA commentary on the ICH guideline for testing for carcinogenicity of pharmaceuticals

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1 | INTRODUCTION

The global regulatory requirements for the assessment of the carcinogenic potential of pharmaceuticals provided for the conduct of long-term carcinogenicity studies in two rodent species, usually the rat and the mouse. Given the their extensive use of animals as well as the costs of these studies, it is in keeping with the mission of International Council on Harmonization of Technical Requirements of Pharmaceuticals for Human Use (ICH) to examine whether this practice requiring long-term carcinogenicity studies in two species could be reduced without compromising human safety.

In August 2022, the ICH issued the final version of the S1B Addendum,[1] describing a novel approach to study the carcinogenic potential of new human pharmaceuticals. In this addendum, a weight-of evidence (WoE) approach that moves away from conducting a 2-year rat study applying a science-based reasoning is explained. Such an approach stipulates that, based on knowledge generally present at the end of phase 2 of pharmaceutical development, that is, the stage when a company will usually decide to conduct a full carcinogenicity programme including a 2-year rat carcinogenicity study, a rat carcinogenicity study might not need to be performed. In this commentary, as a specific group of experts related to the newly established Nonclinical Working Party (NcWP) of the European Medicines Agency (EMA), we seek to outline the likely benefits of this guidance at the occasion of its implementation, jointly with additional European regulatory perspectives on the area of carcinogenicity testing.

2 | HISTORICAL PERSPECTIVE

Potential carcinogenicity of pharmaceuticals has been an important theme on the agenda of European medicines regulatory network discussions since its inception, being included from the start of the ICH discussions. The EU Safety Working Party represented the European Union (EU) in this respect on the first ICH meeting in Brussels in 1991.[2] Carcinogenicity testing was introduced as a requirement for pharmaceuticals between 1950 and 1970, and the introduction of 'Good Laboratory Practice' by the Organization for Economic Cooperation and Development (OECD) in 1979 has led to standardization of the study design. However, in several areas in the world, important difference did exist in the application of this testing requirement, and thus, it was agreed as being the first topic (S1) in the Safety area of the ICH.

After release of the various ICH guidelines, eventually concluded in 1997,[3–5] there was a worldwide continuation in the evaluation of the various transgenic mouse approaches within the framework of the Health and Environmental Research Institute (HESI).[6]

Datasets on carcinogenicity studies from an EU source[7] and an US source[8] promoted a further discussion on the relevance of the 2-year rat study, exemplified in a discussion on the mechanisms of action observed with human pharmaceuticals.[9] It was highlighted that part of this mechanism related to carcinogenicity was the pharmacological action of the compounds.

The Pharmaceutical Research and Manufacturers of America (PhRMA) proposed the NEGCARC approach,[10] where NEG refers to the absence (Negative outcome) of chronic toxicity, Endocrine effects and Genotoxicity. There was a positive reception to this proposal in the EU. An anonymized set of these data was provided by the US Food and Drug Administration (FDA) to EMA, as well as the other participating regulator, the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) within the ICH at that time. These data have been analysed from a pharmacological viewpoint and led to a new hypothesis that the outcome of 2-year carcinogenicity studies in the rat in many cases can be predicted on both the pharmacological and toxicological knowledge available at the end of phase 2. These events paved the way for a renewed ICH S1 Working Group and the publication of the ICH S1 Regulatory Notice Document.[11] This RND explained the conduct of a real-world regulatory experiment, in which companies (sponsors) are invited to submit a Carcinogenicity Assessment Document (CAD), where the expected outcome of the 2-year rat study is predicted, based on an initial WoE assessment. The predictions were assigned to one of three main categories (Table 1).

A dedicated EMA Safety Working Party (SWP) Working Subgroup on Carcinogenicity Assessment has assisted the ICH S1 delegates in the prospective evaluation study (PES) during which the independent review of the CADs was performed. This group assisted also in the evaluation of the PhRMA dataset, which has been extended by similar data from FDA and the Japanese Pharmaceutical Manufacturers Association (JPMA), making a total of 298 compounds.[12] A renewed and extended evaluation of the EU data confirmed the outcome of this study.[13] These analyses have set the tone to highlight the pharmacology of the compounds as a primary factor.

TABLE 1 Risk categories assigned to Carcinogenicity Assessment Documents.

Category 1	Highly likely to be tumorigenic in humans such that a product would be labelled accordingly and 2-year rat carcinogenicity studies would not add value
Category 2	The available sets of pharmacologic and toxicologic data indicate that tumorigenic potential for humans is uncertain and rat carcinogenicity studies are likely to add value to human risk assessment
Category 3a	Highly likely to be tumorigenic in rats but not in humans through prior established and well recognized mechanisms known to be human irrelevant, such that a 2-year rat study would not add value
Category 3b	Highly likely not to be tumorigenic in both rats and humans such that no 2-year rat study is needed

3 | BENEFITS OF THE GUIDANCE

3.1 | Inclusion of the biological target

The ICH S1B(R1) Addendum[1] provides anadditional approach that will contribute to a more science-based drug development. According to ICH S1A,[3] the need to conduct a 2-year carcinogenicity study is based upon the intended duration of clinical treatment, that is, more than 6 months (or intermittently up to 6 months within a short period). The original ICH S1B guidance[4] defines then the choice of species, that is, preferably the rat for a 2-year study, in conjunction with a short- or medium-term study in a second species, usually the mouse. Alternatively, the sponsor might choose to conduct a 'classical' long-term study in mice. The addendum now provides the opportunity to apply a WoE approach based upon scientific reasoning in which the biological target is the first factor to be considered.

The original ICH S1B[4] already explains the usefulness of mechanistic studies for the interpretation of tumour findings to provide a perspective on the relevance for human risk assessment. Rather than a pharmacological emphasis, the guideline mentioned cellular changes that have a toxicological perspective (such as apoptosis, cell proliferation, liver foci of cellular alteration or changes in intercellular communication). Furthermore, hormonal changes (e.g. T3/T4, prolactin, growth factors) are included. From a European point of view, it is welcomed that the new addendum includes a harmonized view of the leading pharmaceutical regulatory authorities with respect to the impact of mechanistic aspects, which is more explicitly related to the pharmacology of a molecule.

ICH S1B[4] provides also some recommendations in relation to equivocal genotoxicity, which are later on included in the ICH guideline S2 (R1).[14]

3.2 | The ICH S1B addendum in the context of reduction of animal use

In the EU, Directive 2010/63/EU on the protection of animals used for scientific purposes,[15] unambiguously fosters the application of the principle of the 3Rs (Replacement, Reduction and Refinement of animal use). Indeed, the Directive clearly states in Art. 4 that EU Member States will ensure that, where possible, animal-free methods or testing strategies shall be used if there is another method or testing strategy for obtaining the result sought.

In addition, reduction and refinement aspects are equally emphasized in Articles 4 and 13 that clearly guide the choice of methods to be used. In September 2020, the strong EU 3Rs culture took a step forward with the release of a resolution by European Parliament calling for a plan to accelerate the transition to innovation without use of animals in research and regulatory testing.[16]

The implementation of the integrative WoE approach as proposed in the S1B addendum addresses 3Rs concerns in the area of carcinogenicity testing, as the focus on the need of a 2-year rat carcinogenicity study will be based upon a comprehensive assessment of available pharmacological, biological and toxicological data in the WoE approach.

The EMA, in its regulatory science strategy to 2025, also emphasizes recommendations to leverage the use of new in vitro and in silico tools such as micro-physiological systems and complex three-dimensional (3D) cell culture assays with human cells. These efforts are coordinated by the EMA 3Rs Working Party to encompass human as well as veterinary medicinal product requirements, covering all animal usage.[17] The ICH S1 addendum also creates potential opportunities to integrate mechanism-based data in the process, hence fostering 3Rs even to a larger extent in line with the EMA regulatory science strategy 2025.

3.3 | Potential impact on animal use

What would be the possible impact of this addendum in terms of animal use? While this estimation was outside the scope of the ICH S1B revision, an estimate could be made on the basis of the outcome of the Prospective Evaluation Study (PES), more specifically by looking at the number of medicinal products categorized as 'irrelevant to human safety' (Category 3), for which a 2-year rat study would not be necessary, in the ICH S1B dataset. In fact, the 'negative' Category 3b had a very good prediction, while the 'positive' Category 3a had a lower degree of prediction.[18] During the PES, only 48 CADs have been submitted for which 45 summary reports have been received by the DRAs involved. However, in the real world, the number of compounds with carcinogenicity studies that came in via the MAA procedure was much higher. In the period between 2013 and 2017, there were 145 compounds submitted to FDA. The profile of those is unknown as yet, but why should it be different from real life reported before?[7,19]

The reduction of animal use as consequence of the implementation of ICH S1B(R1)[1] is very difficult to appraise, and blunt estimations should be avoided. Moreover, to make an estimate of impact on animal numbers based on EU reporting only is not advised taking into account that pharmaceutical development is a global market.

On the basis of the statistical reporting,[20] it can be observed that carcinogenicity testing encompasses approximately 40 K animals used in the EU area over 2015–2019. The numbers reported by Manupello[21] point to a use of a minimum of 65 K rats and mice in 109 carcinogenicity studies conducted for new drug applications approved by the US FDA from 2015 to 2019. These estimates, even when acknowledging their recognized limitations such as an unknown overlap between the two, provide a general delineation of the numbers being discussed globally. Furthermore, although the estimated number of animals used in carcinogenicity studies may appear to constitute a relatively small proportion of the total number used, it is also important to consider the long duration of the studies (up to 2 years) for which the animals are subjected to testing procedures.

As we can only make estimates based on assumptions, we should first be clear about these assumptions: If the pattern of carcinogenicity studies will not be different over time, then we have a figure of more than 60% of long-term studies with negative outcomes in rats.[7,19] If this is the case, then the most critical step will be at the end of phase 2 when the critical mass of data would allow the developer to make the decision to continue the drug development programme without the conduct of in vivo carcinogenicity studies.

4 | PROCEDURE SEEKING FOR REGULATORY ADVICE AT EMA

As outlined in the Addendum of ICH S1B, sponsors are advised to provide a thorough integrated WoE approach on the need for a 2-year rat carcinogenicity study. If this WoE approach leads to the conclusion that a 2-year rat study should not be performed, EMA encourages sponsors to obtain regulatory feedback.

Consulting EMA with this type of request should be done via the routine process of asking for scientific advice (SA).[22] The WoE assessment is to be submitted as part of the EMA SA Briefing document, which is the core document supporting all EMA SA applications. This document should address the different aspects of the WoE approach as outlined in the Section 2.1 of the ICH S1B(R1) addendum (and listed in Figure 1). For additional support regarding the scientific information to be submitted, a preparatory meeting with EMA can be requested within the same SA procedure.

Within the timelines of the scientific advice procedure (40 or 70 days), the Scientific Advice Working Party (SAWP) will be working in conjunction with the NcWP at EMA for the weight of evidence evaluation and the provision of advice on the need to perform carcinogenicity studies. If issues are identified during the discussions, the possibility of a request for further information to the sponsor is foreseen. This would result in an extended (70-day) procedure allowing the sponsor to further clarify specific aspects of the WoE and support reaching a satisfactory conclusion in the final scientific advice letter adopted by EMA's Committee for Human Medicinal Products. It has

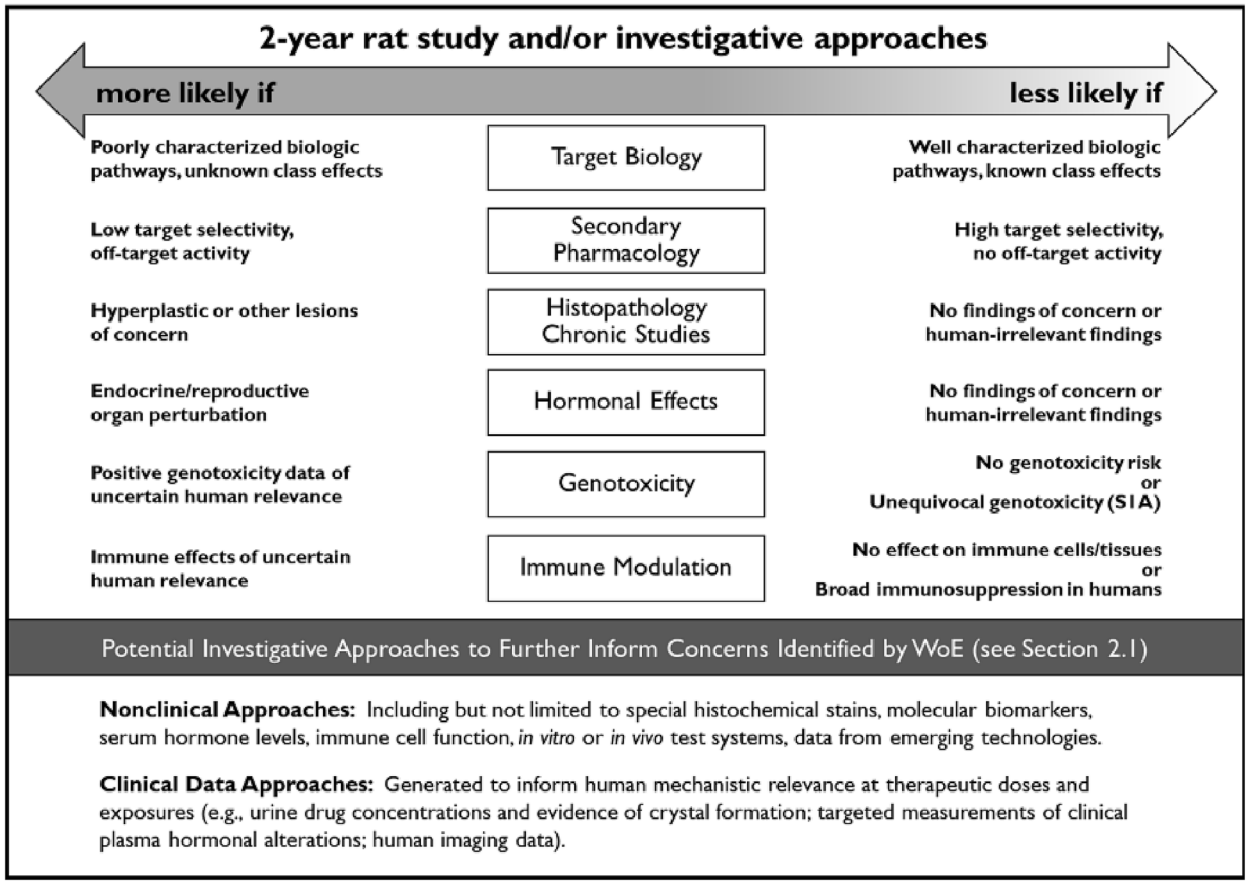

FIGURE 1 Integration of key weight-of-evidence (WoE) factors and potential investigative approaches to further inform on the value of conducting a 2-year rat study for assessment of human carcinogenic risk. When all WoE attributes align towards the right side of the figure, a conclusion that a 2-year rat study would not add value is more likely. Note that for the genotoxicity WoE factor, a 2-year rat study is less likely to be of value either in cases where there is no genotoxicity risk or in cases with unequivocal genotoxicity risk. Similarly, for the immune modulation WoE factor, a 2-year rat study is less likely to be of value in cases where there are either no effects on the immune system or in cases where there is broad immunosuppression.

to be highlighted that the assessment of the sponsor's request at the time of a scientific advice is not legally binding and that the final assessment on the need of a 2-years rat carcinogenicity study will be done during the assessment of marketing authorization application (MAA), after assessors have done the evaluation of the whole MAA data package.

5 | CARCINOGENICITY STUDIES IN EMA SCIENTIFIC ADVICES FROM 2021 TO 2022

After publication of the draft ICH S1B addendum for public consultation in 2021, an increased number of sponsors approached EMA via its Scientific Advice services for questions related to the performance of in vivo carcinogenicity studies. We performed a search in the EMA databases and returned that, during 2021–2022, more than 40 requests were addressed to EMA concerning the need for carcinogenicity studies in vivo.

Broadly speaking, these requests could be clustered in two groups:

1. With requests for deferral of the 2-year rat studies to post-approval (with a 6-month RasH2 Tg mouse study to be provided by the time of MAA; the ICH S1B gives the opportunity to use this specific transgenic mouse strain as a screening model for carcinogenicity testing of human pharmaceuticals, because of its perceived higher sensitivity to detect human carcinogens within 6-month administration)
2. With requests for applying a WoE approach to evaluate the human carcinogenic risk while conducting a rat carcinogenicity study would have no added value

Requests in the first groups were often accepted, mainly due to the nature of the product being developed and/or the specific disease/treatment context of use. Irrespective of the reason for accepting such a deferral request, EMA also asked to provide a WoE approach for carcinogenicity to support such a position at the time of MAA, similarly to what the draft ICH S1B addendum lays out.

The second group of requests fully coincides with the topic of the ICH S1B(R1) addendum, that is, for situations in drug development where a rat carcinogenicity study is not expected to add value to the

human risk assessment. In many cases, and although guideline S1B (R1) was not yet implemented, EMA showed openness to evaluate a WoE approach as per the criteria delineated in the draft guideline Step 2[23] and, where possible, already provided advice in line with this. In other cases, the scientific reasoning for accepting the request not to perform 2-year rat studies was based on pharmaceutical class effects and well-defined mechanisms of action, local routes of administration where no systemic exposure is expected, due to the expected short treatment times or to the endogenous nature of the active substance being developed. For none of these cases, EMA asked for 2-year rat study to be conducted as a default. The agency however rejected requests where components of the WoE assessment were not provided for review.

6 | CONTINUATION OF 2-YEAR MOUSE STUDIES

The 2-year mouse carcinogenicity studies are still being mentioned in the addendum as an option. In the draft addendum undergoing public consultation,[23] the EU medicines regulatory network has explicitly indicated not to agree with this. In the literature, the two species do not carry the same weight, with the rat being more relevant than the mouse. Thus, if under the new S1B rats studies are considered to have no added value, the EU delegation considered the need for mouse studies is not justified.

The use of two species has been criticized from various sides for several decades. In particular, the use of mice was found to be redundant.[24,25] The mouse should also be less suitable because of the high background incidence of spontaneous tumours, as well as the genetic variability between strains. In addition, the mouse has a higher chance of developing liver tumours as compared to rats due to induction of metabolic enzymes.

The ICH S1B guideline[4] already highlights restrictions about the use of mouse carcinogenicity studies for regulatory purposes, that is, the criticism on the position of the 2-year mouse study is reflected in the sequence of the animal models requested in the testing strategy. There is full emphasis on the 2-year rat study, including supportive evidence from studies conducted in genetically modified mouse models. As a last option in the assessment of carcinogenicity risk, the conduct of a 2-year mouse study is requested (see for a review[26]).

An important cornerstone for the use of two different species is the concept of trans-species carcinogenicity.[27] In this concept, the predictivity for humans would be lower if the compound is positive in one species only. When the carcinogenic potential of a compound would be an inherent property of this compound, then it should cause cancer in every species, and in that case, a single species might be sufficient.

Tennant[27] has indicated that compounds that induce tumours in more than one species, in both genders and in more than one organ, have a higher risk for humans as the risk factors are additive. This concept might be true for genotoxic agents, because of their rather unspecific DNA-damaging effect. It is less likely that this is also applicable to non-genotoxic compounds. Antipsychotics, such as risperidone, penfluridol and chlorpromazine, induced tumours in multiple organs by their specific pharmacology (i.e. pancreas, mammary gland and pituitary gland) and in multiple species (i.e. rats and mice).[28] It is generally accepted that these effects are related to the same properties of the compound.

Scientific bases to conduct mouse carcinogenicity studies for human carcinogenic risk assessment have been under debate for a long time.[29,30] Additionally, there have been suggestions that carcinogenicity as a toxicological endpoint is also questioned with a comment that it could be covered by other hazardous property categories in classification, such as mutatoxicity or genotoxicity and organ toxicologic endpoints.[31]

The result of the current addendum's wording is that sponsors are allowed to use a WoE approach for the rat study but irrespectively need to perform either a 6-month transgenic or a 2-year mouse study.

6.1 | Use of genetically modified mice

While a formal statement on the use of various genetically modified animal models for carcinogenicity assessment has been published nearly two decades ago,[32] the EU position has not been revisited since and neither has the role of these models following the ICH S1B addendum publication. During this ICH S1B process, the JPMA has provided scientific support for the exposure ratio that has been accepted as evidence for the ratio of 50 as the limit,[33] which is included in the addendum.

Additionally, the few TgRasH2 studies that were reviewed as part of the ICH S1 PES could not systematically confirm 2-year rat carcinogenicity data. The reasons for that are as follows: (1) Rat is the mainly used species for 6-month repeated dose toxicity studies with full histopathological and other metabolic data, and (2) 6-month rat repeated dose toxicity studies with all toxicological data were also used as a main reference data bank for human cancer risk assessment in the PES. All of these issues guided the EU to focus only on in vivo carcinogenicity studies—if truly needed—to be conducted with rats. The other in vivo data from non-rodents were considered as complementary only. Altogether, in line with this critical science-based thinking, EU is more critical compared to other ICH regions towards the use of mice in short- or long-term carcinogenicity studies.[19]

6.2 | Role of genomics in the prediction of carcinogenicity

Due to complexity of pathways that may lead to development of neoplasms in animals and man, and due to huge variation of chemical structures of pharmaceuticals and their mechanisms of actions, it will be a huge challenge to develop easy and fast 'all included' genetic cancer biomarker(s) for human cancer risk assessment in nonclinical settings. However, there are a few examples when biochemical

mechanisms in neoplasm development can be identified to be species specific. For example, development of chemically induced mouse liver tumours via CAR receptor-mediated mechanism that has been considered to be non-relevant to humans.[34]

The role of genomics in the WoE approach for carcinogenicity is still limited but has the potential to contribute to this important purpose. In humans, several cancer disease-based biomarkers have been identified, but their usefulness in preclinical platforms has not been demonstrated. As an example, from a theoretical point of view, one potential approach could be to use different microRNAs and related pathway analysis as cancer/neoplasm detecting biomarkers[35,36] when their relevance has been tested and documented between toxicological species and humans.

At a very detailed level, genomics information can give us insight into events that occur within cells at an early stage following exposure to a substance. If these events are part of a set of events (signature/biomarker) known to occur or to be involved in the process of tumour formation, it can contribute as additional evidence in the WoE approach. This can be of particular importance in cases when other evidence might be limited, for example, where a novel target is involved.

Considerable efforts have been made on identifying these biomarkers in recent years, for example, those involved in the formation of several hormonal related pathways[37] and liver tumours.[38] Duijndam et al[39] have developed a single-cell imaging technique using fluorescent reporter human breast cancer cell lines as an approach for carcinogenic hazard assessment of estrogenic compounds. For the genomics approach to be successful and be a standard and reliable part of the WoE, a set of validated biomarkers and pathway analysis that represent a wide variety of carcinogenic mechanisms in several species including man (in vitro) is required.

In the years that the addendum was taking shape and CADs were being submitted, companies had the opportunity to develop genomic techniques as part of their WoE approach. Unfortunately, the number of genomics-based evidence that was submitted was very limited, which is seen as a missed opportunity. However, further initiatives are being taken to move the field forward.[40] EMA experts welcome evidence provided from new emerging tools (e.g. in vitro, in silico, etc.) early in drug development programmes and in the WoE assessment for carcinogenicity testing and are willing to collaborate with methods developers via the 'Qualification of novel methodologies' channel available at EMA.[41]

7 | OTHER REGULATORY AREAS

Would it be possible to extend this approach to other regulatory areas? An expert group under the auspices of the OECD is working on international consensus on an approach for testing and assessment of chemical non-genotoxic carcinogens. Using the adverse outcome pathway concept, various cancer models and overarching mechanisms were identified. The OECD opened a call for relevant assays in 2018 to receive suggestions, and the intent is to select the best scoring assays for integrated approaches to testing and assessment.[42]

Other initiatives, such as the European Partnership for Alternative Approaches to Animal Testing (EPAA) project on the evaluation of agrochemicals, led by the RIVM in the Netherlands, are exploring this. In 2017, building upon the experience and on the outcomes of the previous EPAA project on the prediction of carcinogenicity of pharmaceuticals and evidence acquired under the ICH S1,[12] the EPAA launched a project to identify opportunities for improving the science supporting the regulatory testing of agrochemicals, and to achieve a reduction in the use of animals when assessing the potential for carcinogenicity. Chiefly the overall aims are to (1) enhance the prediction of carcinogenic potential of agrochemicals in humans using mechanistic information together with 3-month repeated dose toxicity data to reduce or replace the need for 2-year carcinogenicity studies and (2) establish a virtual waiver approach for the 2-year carcinogenicity animal assay for agrochemicals.[43,44]

8 | CONCLUSION

The EU medicines regulatory network welcomes the entry into application of the ICH S1B(R1) addendum, as the opportunity to follow an additional WoE approach. This allows drug developers to forego the conduct of a 2-year rat study on a data-driven basis enhancing the scientific content. This brings the carcinogenicity assessment paradigm in ICH S1B in line with the approaches described earlier in the ICH S6(R1) addendum, increasing consistency of ICH guidelines in this respect.

The ICH S1B(R1) addendum provides a further possibility to achieve 3Rs benefits globally. Companies are encouraged to apply the principles in the new guidance during drug development, enhancing the knowledge on the relation of the biological targets at hand with potential proliferative or non-proliferative mechanisms, and subsequently by interacting with regulatory authorities to obtain recognition of lack of added value of 2-year rat studies. It should be noted, in view of the lack of added value, that the non-conduction of a 2-year rat studies is not to detriment the assessment of the carcinogenic potential of a human pharmaceutical product, which will continue to be carried out in its entirety, ensuring that long-term safety is in no way compromised.

EU regulators are already providing scientific advice based on the addendum consistent with its recent positions on rodent carcinogenicity studies. Genomics and novel 3R methods are likely to gain further traction in informing carcinogenic risk of pharmaceuticals and, possibly, other products regulated under other frameworks (e.g. agrochemicals). Data emerging from these techniques could further obviate the need for the conduct of 2-year rodent carcinogenicity studies.

AUTHOR CONTRIBUTIONS

All authors were involved in the conception and design of the article, review of the literature and the drafting and final approval of the manuscript.

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None.

CONFLICT OF INTEREST STATEMENT

All authors declare that they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data underlying this review can be accessed using the listed references or are available upon reasonable request.

ETHICS STATEMENT

The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the regulatory agency/agencies or organizations with which the authors are employed/affiliated.

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