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Research article

Results from an EFPIA, JPMA, PhRMA industry survey on reopening and revamping the ICH S7A guidance on safety and secondary pharmacology

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ABSTRACT

The ICH S7A guideline on safety pharmacology has remained unchanged since its inception in 2000, fulfilling its crucial role in safeguarding clinical trial participants and patients (ICH S7A). However, in the meanwhile there has been significant scientific and technological advancements in drug safety science, a paradigm shifts of the drug discovery and development process, and an continuously evolving regulatory landscape, that led to the recommendation to revisit, adapt and evolve the ICH S7A guideline (Valentin & Leishman, 2023, 2025). A revision of the guidance would imply opening an ICH process, the first step consists in the development of a 'concept paper'. In that context, a survey has been developed to determine which elements, if any, of the ICH S7A guideline should be revised. Sixty-five (65) responses were obtained from industry representatives of companies affiliated to EFPIA, JPMA or PhRMA. Overall, there was a large support to revisit most of the pillars originally identified via a 'revision' or a 'Q&As' ICH procedure. These include revisiting the 'core battery' assessment (58 to 68 %), the adversity concept (77 %), the modality agnosticism of the guideline (89 %), the in vitro secondary pharmacology component (85 %), the integrated risk assessment principles (75 %), and the inclusion of safety pharmacology endpoints in general toxicology studies (72 %). However, there were fewer than 50 % positive responses to revisiting the timing of the studies with respect to drug development stages and the validation or qualification principles to be applied to novel assays and models (<50 % of positive responses). Notably, the majority of respondents viewed the 'core battery' studies as valuable, whereas 'supplemental' studies were less frequently seen as contributing additional value. Moreover, many indicated that they routinely perform safety pharmacology studies outside of these predefined categories—such as exploratory, mechanistic, or investigative studies. Overall, there was a large agreement between the responses from all territories. The survey results captured which elements of the ICH S7A guideline should be revised to help the development of a formal ICH concept paper.

Abbreviations: ADC, Antibody-Drug Conjugate,;3Rs; The principles of Replacement, Reduction and Refinement; ACT, American College of Toxicology; CiPA, Comprehensive In vitro Proarrhythmia Assay; CNS, central nervous system; EFPIA, European Federation of Pharmaceutical Industries and Associations; HESI, Health and Environmental Sciences Institute; ICH, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; IQ, International Consortium for Innovation and Quality in Pharmaceutical Development; JPMA, Japan Pharmaceutical Manufacturers Association; NAMs, New Approach Methodologies or Non Animal Methodologies; NBEs, New Biological Entities; NCEs, New Chemical Entities; NOAEL, No Observed Adverse Effect Level; PDEG, Pre Clinical Development Group; PhRMA, Pharmaceutical Research and Manufacturers of America; Q&As, Questions and Answers; TPD, Targeted Protein Degrader.

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1. Introduction

In 2025, the ICH S7A guideline on safety pharmacology mark the 25th anniversary since its release (ICH, 2000). Over this period, it has remained unchanged, continuing to play a critical role in safeguarding clinical trial participants and patients (Valentin & Leishman, 2023 & 2025; Valentin, Sibony, Rosseels, & Delaunois, 2023). However, substantial scientific advancements, technological innovations in drug safety science, a paradigm shift in the drug discovery and development process, and an ever-evolving regulatory landscape underscore the need to revisit and modernize the ICH S7A guideline (Valentin & Leishman, 2023 & 2025; Valentin et al., 2023). Beyond some initial recommendations by Guth and Pugsley (2017) and Baldrick (2021), the proposal from Valentin and Leishman (2023) to revamp ICH S7A was presented at several forums, where it has been met with enthusiastic support and constructive feedback from stakeholders, practitioners, regulators, and the broader scientific community (van den Berg & Aylward, 2024). During a well-attended webinar hosted by the *Safety Pharmacology Society* on 13th July 2023, 73 % of respondents supported the need to revise the ICH S7A guideline (Fig. 1). By the end of the webinar, after arguments were presented, this figure rose to 90 % (see link: Safety Pharmacology Society). Further evidence of growing interest came during the *American College of Toxicology* (ACT) symposium held on 21st November 2024, entitled *"Revamping ICH S7A: Time for Change?"*. The event included a panel discussion featuring representatives from pharmaceutical companies and regulatory agencies worldwide (see link: ACT_2024_Symposia and Workshops). A poll conducted among the attendees revealed that over 90 % of participants favoured revising the guideline (Fig. 1). Ahead of the ACT symposium the authors conducted a survey among representatives of pharmaceutical companies *"to determine which elements, if any, of the ICH S7A guideline should be revised"*. The results are presented in this article. Furthermore, we discussed the survey results and next steps moving toward a revision of the ICH S7A guideline. A revision of the guidance would imply opening an ICH process, the first step consisting in the development of a 'concept paper' (ICH Official web site: ICH).

2. Methods

During the summer of 2024, thirty (30) questions were distributed via SurveyMonkey™ to pharmaceutical companies affiliated with EFPIA, JPMA, and/or PhRMA trade associations. To maximize participation, the survey was shared through EFPIA-PDEG, IQ-DruSafe, HESI, and JPMA. Respondents were encouraged to review and refamiliarize themselves with ICH S7A, S7B, and the relevant Questions and Answers (Q&As) before completing the survey. Only one response per organization and territory was expected, except in cases of territory-specific considerations. The survey was designed to take only a few minutes to complete. The full set of survey questions is reported in Table 1. The first

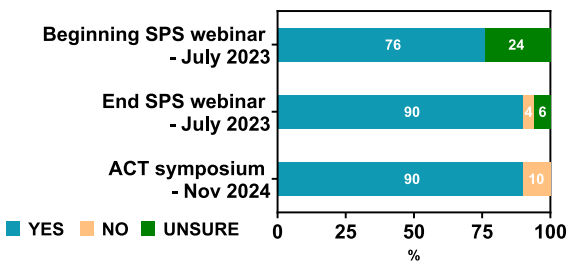

Fig. 1. Poll results to the question *"Do you believe the time has come to revamp the ICH S7A?"* conducted during a *Safety Pharmacology Society* (SPS) webinar held on 13th July 2023 and the *American College of Toxicology* (ACT) symposium held on 21st November 2024. The SPS webinar and ACT symposium was attended by over 100 and 300 participants, respectively. The results illustrate the strong support from the audience to revamp the ICH S7A guideline.

three questions collected respondent identification details, company affiliation, and trade association or territorial membership. These were used for potential secretariat follow-up but were excluded from the blind compilation. The fourth question provided insight into the respondents' companies portfolio focus from a modality perspective. A total of 21 questions (questions 5–20 and 24–28) featured multiple-choice answers, allowing respondents to select only one of three options (Yes, No, Unsure). Seven (7) of these (Q6, Q8, Q10, Q12, Q15, Q25, and Q28) served as follow-ups to Q5, Q7, Q9, Q11, Q14, Q24, and Q27, respectively. Questions 21, 22, 23, and 29 also included multiple-choice options, with the possibility of selecting multiple answers for Q21, Q22, and Q23. The final question (Q30) featured a free-text option, enabling respondents to clarify answers or provide additional comments. From the outset, it was agreed that survey results would be disseminated via communications and publication. Results are presented as absolute numbers or percentages of the total number of responses received per question.

3. Results

A total of 65 responses were collected from companies across three regions or trade associations, with a notably strong response from companies primarily affiliated with the JPMA. Based on 2023 revenue data (chemanalyst.com/ChemAnalyst/PharmaCompanies), the respondents were evenly distributed across small, mid, and large-sized companies, defined arbitrarily by revenue categories as follows: US $ <1B, 1-10B, and > 10B, respectively (Fig. 2). Most survey questions were answered by all respondents, except for follow-up questions (Q6, Q8, Q10, Q12, Q15, Q25, and Q28), which were contingent on responses to prior questions (Table 1).

From a portfolio perspective, the organizations represented in the survey focused on a range of products, including traditional New Chemical Entities (NCEs; e.g., small molecule drugs; 83 %), New Biological Entities (NBEs; e.g., antibodies, bi- and tri-specific antibodies; 51 %), and novel modalities such as next-generation peptides, targeted protein degraders, gene therapies, vaccines, oligonucleotides therapeutics, proteins, and antibody-drug conjugates. Each of these categories accounted between 20 and 34 % of the responding companies (Fig. 3).

As illustrated in Fig. 4, there was substantial support among respondents for revisiting and clarifying safety pharmacology evaluations of novel modalities (Q5; 69 %). Support was also strong for updating the core battery assessments (central nervous, cardiovascular and respiratory systems) with the following positive responses of Q7 (67 %), Q9 (68 %), and Q11 (58 %), respectively. Respondents expressed a favourable view to revisit and clarify the concepts of adversity (Q13: 77 %), in vitro secondary pharmacology assessments (Q16: 85 %), including for novel modalities (Q17: 69 %), and the integrated risk assessment or weight of evidence approach, including related concepts such as 'margin of safety' (Q19: 77 %). There was also notable agreement for clarifying the incorporation of safety pharmacology endpoints into toxicology studies (Q27: 72 %). When asked about sharing experiences to address these challenges, most respondents expressed a willingness to do so or were unsure about it (Fig. 4). However, fewer respondents considered addressing the timing of safety pharmacology studies in relation to drug development stages (Q14: 46 %) critical, as well as the validation and qualification of novel assays or models (Q20: 18 %; Fig. 4).

Regarding the core battery organ systems, the cardiovascular, central nervous, and respiratory systems were considered most valuable by decreasing order of importance, receiving positive responses from 95 %, 71 %, and 50 % of respondents, respectively (Fig. 5A). Among the supplemental organ systems, shown in Fig. 5B, drug abuse studies were the only ones deemed valuable by a majority (Q22: 58 %).

The motivations for conducting supplemental studies were diverse and included factors such as the primary target, therapeutic areas, modalities, regulatory requests, findings from toxicology studies, and competitive intelligence—each influencing between 55 % and 77 % of respondents (Fig. 5C). Additionally, 63 % of respondents (Q24) reported

Table 1
List of survey questions and associated options for answers and number of responses.

Question number	Question	SC or MC	Plausible answers			Number of responses
Q1	Respondent Name	NA	BLINDED DATA			65
Q2	Organization Name	NA	BLINDED DATA			65
Q3	Trade association / territory affiliation	SC	EFPIA, PhRMA, JPMA, Other			65
Q4	What is the primary focus of your activity? (tick all that apply)	MC	Traditional NCEs: e.g., small molecule drugs; Traditional NBEs: e.g., antibodies, bi- and tri-specific antibodies; Novel Modalities: e.g., Protein degraders, next generation peptide, Gene therapy, vaccines, Oligonucleotides, Proteins, Antibody drug conjugates, Other			65
Q5	The ICH S7A, released in 2000, focuses primarily on traditional small molecule drugs. Some other guidelines partially refer to safety pharmacology (e.g., ICH S6, S9, M3). Should clarity be provided regarding the safety pharmacology evaluation of other modalities (e.g., traditional NBEs, novel modalities)?	SC	Yes	No	Unsure	65
Q6	If you answered yes to the previous question, would you be willing to share how you conduct safety pharmacology evaluations for a given modality?	SC	Yes	No	Unsure	49
Q7	The ICH S7A refers to prescriptive assays and technology platforms for central nervous system (CNS) assessment (e.g., FOB, modified Irwin's test). Should clarity be provided regarding the use of alternative assays and technology platforms (e.g., NAMs) to assess CNS function?	SC	Yes	No	Unsure	64
Q8	If you answered yes to the previous question, would you be willing to share how you conduct CNS safety pharmacology evaluations using these alternative assays and technology platforms?	SC	Yes	No	Unsure	48
Q9	The ICH S7A refers to prescriptive assays and technology platforms for cardiovascular system assessment (e.g., blood pressure, heart rate, electrocardiogram). Should clarity be provided regarding the use of alternative assays and technology platforms (e.g., NAMs) to assess cardiovascular function?	SC	Yes	No	Unsure	65
Q10	If you answered yes to the previous question, would you be willing to share how you conduct cardiovascular safety pharmacology evaluations using these alternative assays and technology platforms?	SC	Yes	No	Unsure	49
Q11	The ICH S7A refers to prescriptive assays and technology platforms for respiratory system (e.g., respiratory rate and other measures of respiratory function). Should clarity be provided regarding the use of alternative assays and technology platforms (e.g., NAMs) to assess respiratory function?	SC	Yes	No	Unsure	65
Q12	If you answered yes to the previous question, would you be willing to share how you conduct respiratory safety pharmacology evaluations using these alternative assays and technology platforms?	SC	Yes	No	Unsure	43
Q13	The ICH S7A refers to 'adverse' effects numerous times without providing a definition. Should clarity be provided regarding the term 'adverse' in the context of safety pharmacology studies?	SC	Yes	No	Unsure	65
Q14	The ICH S7A describes the timing of safety pharmacology studies in relation to drug development phases, supporting first-in-human trials, clinical trial participants, and patient post-approval. The ICH E14/S7B Q&As illustrate how different integrated assessments occur at different phases of clinical development. Should clarity be provided regarding the scope, focus, and timing of other safety pharmacology evaluations?	SC	Yes	No	Unsure	65
Q15	If you answered yes to the previous question, would you be willing to share how you determine the scope, focus, and timing of safety pharmacology evaluations in relation to drug development phases?	SC	Yes	No	Unsure	35
Q16	The ICH S7A has limited references to secondary pharmacology (also known as in vitro off-target profiling or pharmacological profiling), which is increasingly considered important in drug safety. Should clarity be provided on the contribution and use of in vitro secondary pharmacology to support the safety evaluation of drugs?	SC	Yes	No	Unsure	65
Q17	Traditionally, secondary pharmacology has been addressed through binding and functional assays. However, novel modalities may present different off-target secondary pharmacology opportunities using in vitro/in silico assays (e.g., off-target hybridization for ASOs, inhibition of protein degradation for TPD, cell microarray for monoclonal antibodies). Should clarity be provided on the secondary pharmacology approaches for novel modalities?	SC	Yes	No	Unsure	65
Q18	If you are experienced in addressing the secondary pharmacology of novel modalities, would you be willing to share your approaches?	SC	Yes	No	Unsure	61
Q19	The concept of 'integrated risk assessment' was recently incorporated as a pivotal component of the ICH E14/S7B Q&As (2022). Should the concept of integrated risk assessment, or a weight of evidence approach and associated concepts such as 'margin of safety' be incorporated into a revised ICH S7A?	SC	Yes	No	Unsure	65
Q20	The ICH E14/S7B Q&As describe principles for validation, qualification and assays best practices (i.e., to demonstrate statistical and assay sensitivity) for a given context-of-use required for regulatory acceptance and decision-making. Should the same principles be applied across all aspects of safety pharmacology?	SC	Yes	No	Unsure	65

(*continued on next page*)

Table 1 (*continued*)

Question number	Question	SC or MC	Plausible answers			Number of responses
Q21	Of the safety pharmacology activities, which of the core battery studies do you consider as adding value, irrespective of the modality?	MC	Central nervous system	Cardiovascular system	Respiratory system	56
Q22	Of your safety pharmacology activities, which of the supplemental studies do you consider as adding value?	MC	Renal/Urinary system, Autonomic nervous system, Gastrointestinal system, Immune system, Endocrine system, Drug abuse liability (dependency potential), Skeletal muscle system, Other (please specify)			38
Q23	Is the choice of supplemental studies driven by:	MC	primary target, therapeutic areas, modalities, other (e.g., regulatory request, toxicology studies findings, competitive information)			64
Q24	Do you employ additional assays beyond the S7A core or supplemental studies (e.g., exploratory, mechanistic, investigative)?	SC	Yes	No	Unsure	65
Q25	If yes to the previous question, would you be willing to share?	SC	Yes	No	Unsure	44
Q26	In recent years, novel challenges have emerged (e.g., new modalities, route of delivery). Should a framework be developed, as part of the guidance, to help sponsors and regulators define and design the optimal safety pharmacology evaluation to meet these novel challenges?	SC	Yes	No	Unsure	65
Q27	ICH S7A parameters are already being incorporated in the repeat dose toxicology studies. Should there be guidance on enabling such an approach for regulatory decision making?	SC	Yes	No	Unsure	65
Q28	If you answer Yes to the previous question, would you be willing to share your approaches?	SC	Yes	No	Unsure	65
Q29	Based on your understanding of the ICH process (ICH-maintenance-procedure), ICH S7A, sister guidance S7B, and the current questionnaire, what approach would you recommend for revisiting the S7A?	SC	Q&As procedure, Revision procedure, Maintenance procedure, Unsure			65
Q30	If you have any questions or suggestions other than those listed above, please feel free to write them here.	NA	Open field text			27

Q, Question, NA, Not Applicable; SC, Single Choice; MC, Multiple Choice.

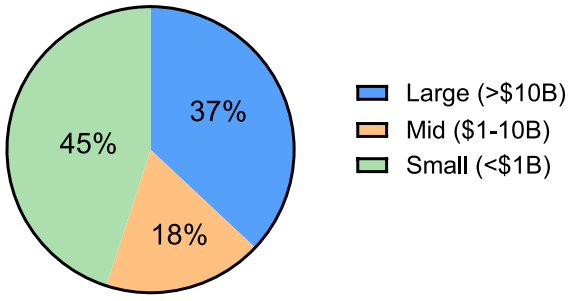

Fig. 2. Distribution of survey-contributing companies (Q2) based on 2023 revenues (chemanalyst.com/ChemAnalyst/PharmaCompanies). Respondent organizations were evenly distributed across small, mid, and large-sized companies, categorized by the 2023 revenue of < US $1B, between US $1 and 10B, and > US $10B. A total of 65 companies responded to the survey.

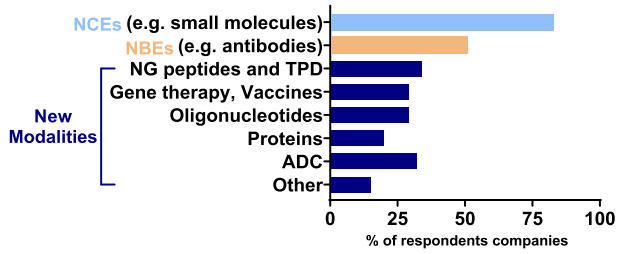

Fig. 3. Portfolio emphasis of survey-responding companies (Q4). The surveyed organizations represented a diverse range of product modalities, including traditional new chemical entities (NCEs; e.g., small molecules), new biological entities (NBEs; e.g., monoclonal, bi-, and tri-specific antibodies), and emerging modalities such as target protein degraders (TPD), and next-generation peptides, gene therapies, and vaccines, proteins, and antibody-drug conjugates (ADC). A total of 191 responses were obtained from 65 companies indicating that most companies operate across multiple modalities.

conducting additional safety pharmacology studies beyond the core battery and supplemental categories such as exploratory, mechanistic, or investigative studies (Fig. 5D).

In light of current ICH procedures, the ICH S7A guidance, and the findings of the current survey, respondents suggested that the ICH S7A guideline be revised, via a revision procedure followed by a Q&A procedure to address emerging issues (Q29: 48 % and 37 %, respectively; Fig. 6).

To the last question, 16 respondents offered free-text comments. A common theme emerged regarding the urgent need to update S7A through a single, integrated guidance that incorporates both in vitro (secondary pharmacology) and in vivo approaches while maintaining flexibility in relation to therapeutic modality or areas; For example, S6 addresses modalities (i.e., biologics), while S9 is focused on oncology. Several emphasized the importance of ensuring alignment with existing guidelines, particularly M3(R2), S6, S9, and S13, to promote consistency across regulatory frameworks. Additionally, respondents highlighted the need for greater clarity on specific aspects, such as the influence of gender and age, the timing of measurements, and the distinction between acute and chronic studies. There was also strong support for addressing new modalities by integrating emerging technologies and novel scientific approaches to better reflect advancements in the field.

4. Discussion

A survey conducted under the auspices of three pharmaceutical trade associations (EFPIA, JPMA, and PhRMA) consisting of 30 questions garnered 65 responses. The results revealed widespread support (58 % to 90 %) for revisiting key elements originally identified in Valentin & Leishman (2023, 2025) via a 'revision' or 'Q&A' procedure within ICH guidelines. These elements include reassessing the 'core battery,' the concept of adversity, the modality-agnostic nature of the guideline, the in vitro secondary pharmacology component, integrated risk assessment principles, and the inclusion of safety pharmacology (SP) endpoints in toxicology studies. However, some reluctance was noted regarding revisiting the timing of studies relative to drug development stages and the validation and qualification principles applied to novel assays and

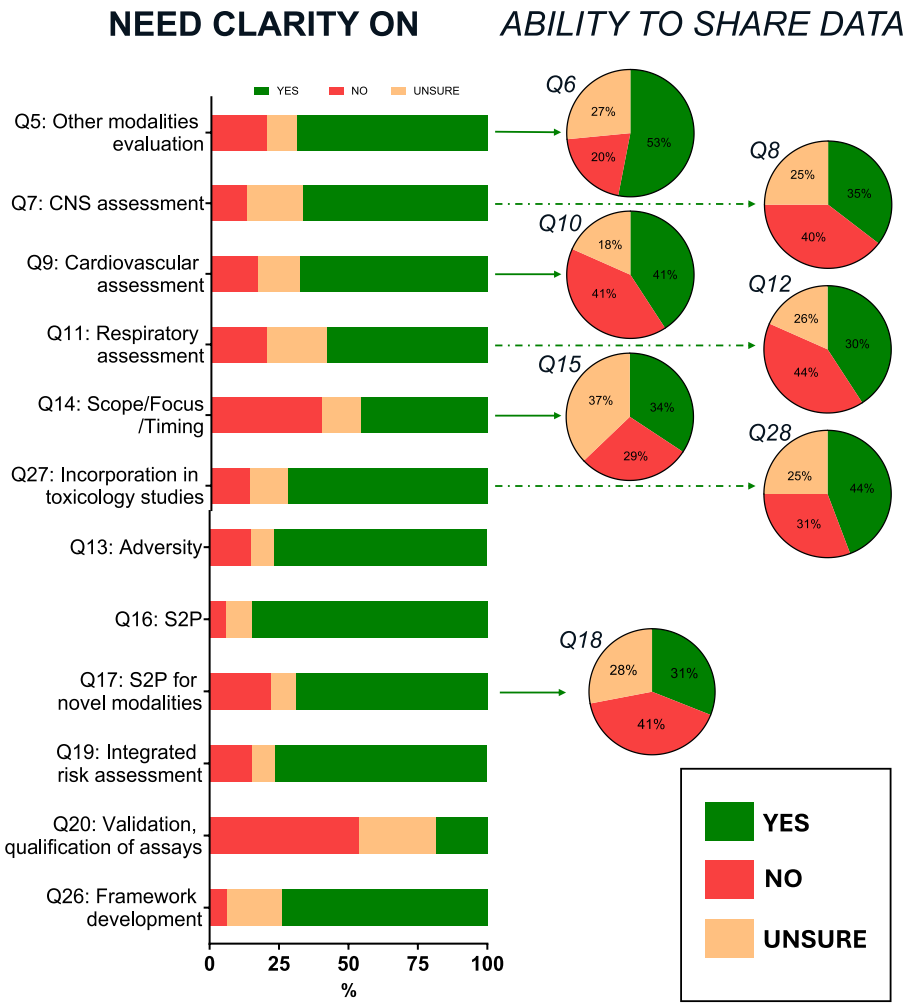

Fig. 4. Perceived need for clarity and willingness to share experiences on ICH S7A-relevant topics. Respondents broadly supported revisiting and clarifying safety pharmacology pillars identified in the survey (Q5, Q7, Q9, Q11, Q13, Q16, Q17, Q19, Q26 and Q27). However, there was less consensus on the need for updates regarding the timing, scope, and focus of safety pharmacology studies (Q14), as well as the principles for validation and qualification of assays (Q20). When asked about sharing, most respondents expressed a willingness to share experiences to address these challenges or were unsure about it (Q 6, Q8, Q10, Q12, Q15, Q18, Q28).

models. Notably, many respondents expressed the value of conducting additional safety pharmacology studies beyond the 'core battery' and 'supplemental' studies (e.g., exploratory, mechanistic, and investigative studies) in support of their drug discovery and development programs. Despite these differences, there was strong consensus across key geographical territories (data not shown), affirming the survey's robustness and relevance. Overall, the results underscore the need to revise the ICH S7A guideline and contribute to the development of a concept paper as the first step in the formal ICH procedure.

Given the significant scientific and technological advances in drug safety science, the paradigm shift in drug discovery and development, and the evolving regulatory landscape, there is a compelling case to revisit and adapt the ICH S7A guideline on safety pharmacology (Valentin & Leishman, 2023, 2025), as previously suggested by Guth and Pugsley (2017) and Baldrick (2021). Such an evolution could streamline the guideline, support the selection of optimized drug candidates, improve confidence in their success, and enhance clinical monitoring throughout all development stages. Additionally, refining the guideline would improve benefit-risk assessments and promote alternative approaches in line with the 3Rs principles on animal use (Valentin & Leishman, 2023, 2025).

4.1. Survey demographics

The survey demographics demonstrated diversity in respondents, representing companies of various sizes, from small to large, based on 2023 revenues. This strengthens the credibility of the data, making it a robust and representative dataset of the global pharmaceutical industry, despite the large number of companies worldwide (>5000; crossriverth erapy.com). Since the Step 4 ratification of ICH S7A in 2000, the pharmaceutical landscape has diversified beyond the traditional new chemical entities (NCEs) and new biological entities (NBEs) initially covered by the guideline (ICH, 2000; Blanco & Gardinier, 2020; Valentin & Leishman, 2023, 2025). The survey confirmed this trend (Fig. 3), with respondents representing a wide portfolio of both traditional and novel modalities, highlighting the need to update S7A to ensure its modality-agnostic nature and facilitate the integration of emerging therapeutic approaches.

4.2. Core and supplemental safety pharmacology studies

A significant portion of respondents (58–68 %) supported revisiting and clarifying the assessment of cardiovascular, respiratory, and central nervous system (CNS) functions—the three 'core battery' physiological domains—by incorporating alternative assays and technology

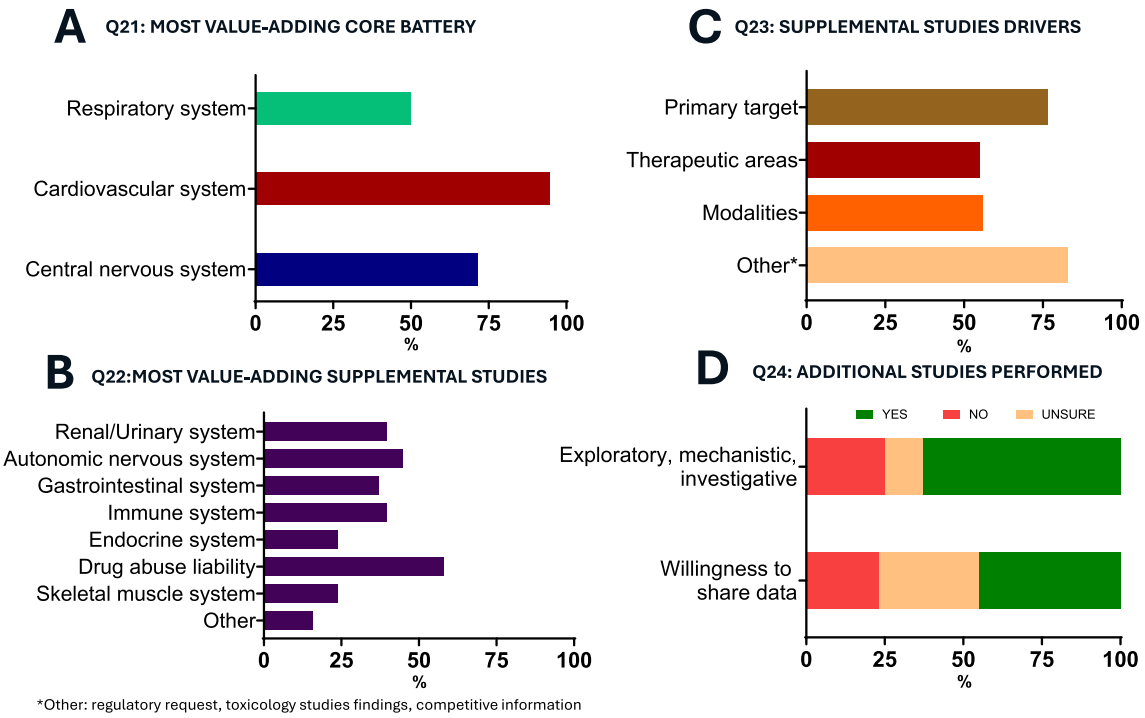

Fig. 5. Perceived adding value of core battery (Q21; panel A) and supplemental (Q22; panel B) safety pharmacology studies. Drivers for conducting supplemental safety pharmacology studies (Q23; panel C). Employment of additional studies beyond core and supplemental assessments (Q24; panel D).

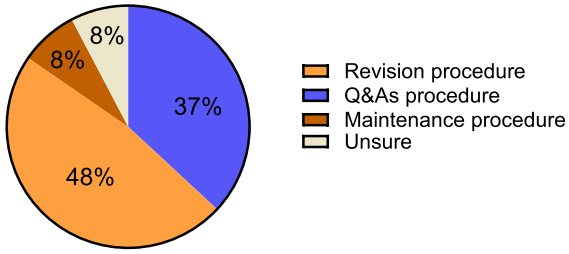

Fig. 6. Respondents' recommendations regarding ICH options to revisit the ICH S7A guideline. Survey participants favoured either a formal revision procedure of the guideline or a Q&As procedure under ICH to address key updates.

platforms, such as new approach methodologies (NAMs). When asked which core battery organ system assessments were most valuable, cardiovascular function emerged as the most supported (95 %), followed by CNS (71 %), with respiratory function receiving much less support (50 %). Furthermore, the routine assessment of 'supplemental' organ systems described in ICH S7A was generally not considered valuable, with positive responses ranging from 16 % to 45 %, except for drug abuse assessments, which garnered 58 % support. The decision to conduct supplemental studies appeared to be influenced by factors such as knowledge of the primary target, therapeutic areas, modalities, competitive landscape, regulatory requests, and toxicology findings. Notably, many respondents reported conducting additional studies, such as exploratory or mechanistic investigations, although the rationale behind these decisions was beyond the scope of the survey and largely undisclosed. This suggests that such studies may provide a competitive advantage to the organizations involved.

There was strong support for clarifying the integration of core safety pharmacology assessments into repeat-dose toxicology studies, potentially enabling regulatory decision-making without the need for standalone safety pharmacology studies. While non-animal approaches should be encouraged, in vivo studies remain essential for assessing safety pharmacology (ICH, 2000; Harrell et al., 2024; Valentin et al., 2023; Valentin & Leishman, 2025). Furthermore, advancements in technology, such as telemetry and non-invasive imaging, provide opportunities to collect high-quality data with minimal animal use while improving animal welfare. Emerging assays must demonstrate human biological relevance, robustness, and sensitivity to detect human-relevant effects (Trepakova, Koerner, Pettit, & Valentin, 2009; Valentin et al., 2009).

4.3. *Clarification of 'adversity' in safety pharmacology studies*

A notable 77 % of respondents expressed support for clarifying the term 'adverse' in the context of safety pharmacology studies. This finding aligns with the absence of a formal definition of adversity in the ICH S7A guideline, despite the term being used 26 times (ICH, 2000). A recent expert review highlighted this gap, noting the absence of clear guidance on determining the No Observed Adverse Effect Level (NOAEL), which is a critical parameter in safety evaluation (Authier et al., 2021; Mow et al., 2020; Palazzi, Burkhardt, Caplain, et al., 2016). Experts have suggested moving away from rigid definitions of adversity and NOAELs, instead proposing a more flexible approach based on integrated risk assessments that account for context and severity (Authier et al., 2021; Mow et al., 2020). This approach would enable a more comprehensive understanding of pharmacodynamic effects across dose levels and exposure.

4.4. *Timing of safety and secondary pharmacology studies*

The ICH S7A guideline outlines the timing of safety pharmacology studies within the context of drug development phases, including first-in-human trials and post-approval monitoring. Survey responses on whether greater clarity should be provided regarding the scope and timing of other safety pharmacology evaluations were divided, with 46 % in favor and 40 % opposed. This diversity of opinion may reflect varying approaches across organizations regarding the deployment of safety pharmacology studies at different phases of drug development.

4.5. In vitro secondary pharmacology test systems

While the ICH S7A guideline provides limited guidance on secondary pharmacology (also known as in vitro off-target profiling), this area has gained increasing importance in drug safety (Bowes et al., 2012; Brennan et al., 2024; Dodson et al., 2021; Jenkinson, Schmidt, Rosenbrier Ribeiro, Delaunois, & Valentin, 2020; Papoian et al., 2015). Unsurprisingly, 85 % of respondents agreed on the need to clarify the role of in vitro secondary pharmacology in drug safety evaluations. The guideline's current references to secondary pharmacology lack consistency, ranging from vague mentions to highly prescriptive requirements (Valentin & Leishman, 2025). A significant portion of respondents (69 %) supported providing clarity on secondary pharmacology approaches for novel modalities, aligning with the broader expansion of portfolios beyond traditional NCEs. The integration of NAMs into regulatory submissions offers an opportunity to refine safety evaluations in line with the 3Rs principles (Avila et al., 2020; Stresser et al., 2024) and improve their value in regulatory decision making (Simpson, Bourcier, & Sadrieh, 2025).

4.6. Integrated risk assessment, weight of evidence, and margin of safety

Integrated risk assessment is a pivotal component of ICH E14/S7B Q&As (ICH, 2022a) and has gained importance across ICH guidelines, such as ICH S1B(R1) (ICH, 2022). Over 75 % of respondents supported clarifying the role of integrated risk assessment or a weight-of-evidence approach in ICH S7A revisions. Integrated risk assessment involves evaluating the totality of evidence, including pharmacodynamics, Pharmacokinetics/Pharmacodynamics relationships, and emerging endpoints, to establish a margin of safety. Respondents emphasized the importance of this approach across various therapeutic modalities and the need to adapt it as new data, including from NAMs, in vitro systems, and in silico models, become available.

4.7. Validation and qualification of novel models and assays

The principles for validation and qualification of novel models and assays, as described in the ICH E14/S7B Q&As (ICH, 2022a), are critical to regulatory acceptance. When asked whether these principles should be clarified across all safety pharmacology aspects, 54 % of respondents opposed the proposal, and 27 % were unsure. The reluctance may stem from concerns about overregulation, potentially stifling innovation in assay development. However, a balanced approach, such as tiered validation frameworks, may allow for the adoption of novel assays while ensuring regulatory acceptance. The example of the hERG assay, a NAM used to identify proarrhythmia risk, illustrates how validation processes can evolve and be integrated into regulatory frameworks (ICH, 2005; ICH, 2022a; Rampe & Brown, 2013).

4.8. Options for evolving ICH guidance

Survey respondents were asked to recommend a procedure for revising ICH S7A. Forty-eight percent favoured a revision, while 37 % preferred a Q&A approach. Both procedures are viable, but considering the scope of emerging complexities, a full revision may be more appropriate. Regardless of the method, the initial step is the development of a concept paper, which outlines proposed changes. The Q&A procedure offers a faster, more immediate response, while the revision procedure results in a more comprehensive update to the guideline.

4.9. General comments

Sixteen respondents provided additional comments, emphasizing the need for a unified guidance that integrates in vitro (secondary pharmacology) and in vivo approaches while maintaining flexibility. Respondents also highlighted the importance of aligning the update with existing guidelines (e.g., M3(R2), S6, S9, and S13) to ensure consistency. Additionally, comments suggested addressing new modalities and incorporating emerging technologies into the revised guidance.

4.10. Conclusion

The survey results strongly support revisiting and clarifying key aspects of the ICH S7A guideline, including the 'core battery' assessment, the adversity concept, modality-agnosticism, the in vitro secondary pharmacology component, integrated risk assessment principles, and the inclusion of safety pharmacology endpoints in toxicology studies. While some reservations were expressed regarding the timing of studies and the validation principles for novel assays, respondents generally expressed enthusiasm for updating the guideline to reflect the latest scientific advances and evolving industry practices. These findings provide a clear path for developing a formal ICH concept paper to guide future revisions of the ICH S7A guideline.

CRediT authorship contribution statement

Jean-Pierre Valentin: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Katsuyoshi Chiba:** Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Derek J Leishman:** Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Emma Pawluk:** Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Hugo M. Vargas:** Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Takashi Yoshinaga:** Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. The authors declare that they are employed by pharmaceutical companies and as such may have access to shares and/or stocks options which may be considered as potential competing interests.

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Data availability

No data was used for the research described in the article.

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