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Points to consider for revising the ICH S7A guideline on safety and secondary pharmacology

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ABSTRACT

Although the ICH S7A guideline on safety pharmacology largely achieved its objective, a proportion of remaining adverse drug reactions and attrition can be attributed in part to gaps in safety and secondary pharmacology assessments. Advances in science, technology, drug development paradigm and regulatory practices necessitate revisiting and evolving ICH S7A to address these limitations. The anticipated completion of the ICH S7B Q&As by end of 2025 provides an opportunity to integrate its outcomes with ICH S7A into a comprehensive, modality-agnostic sustainable over time framework. Such consolidation could streamline guidance, enhance usability, and align regulatory expectations globally. This proposed revision should aim to address key aspects of safety and secondary pharmacology, including the definition of adversity, the integration of human-relevant *in vitro* and *in silico* models, and the adoption of state-of-the-art *in vivo* platforms. Further considerations should include the development of principles for model and assay validation, the promotion of integrated risk assessment frameworks, and incorporation of weight of evidence approaches. Revised guideline would also emphasize sustainable practices by adapting to evolving therapeutic modalities, while reducing reliance on animal testing through New Approach Methodologies. The revision seeks to enhance the benefit-risk evaluation of drug candidates, refine clinical monitoring, foster regulatory acceptance, and streamline drug development. This comprehensive update has the potential to not only optimize drug safety evaluations but also to align industry practices with modern scientific advancements and ethical considerations, ensuring a more robust and efficient pathway for therapeutic innovation.

1. Introduction

In 2025, the ICH S7A guideline on safety pharmacology will 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 and Leishman, 2023; Valentin et al., 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 and Leishman, 2023; Valentin et al., 2023; Guth and Pugsley, 2017; Baldrick, 2021). Beyond the initial recommendations by Valentin and Leishman (2023), that built on prior published literature (Guth and Pugsley, 2017; Baldrick, 2021), the proposal 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 and Aylward, 2024, Fig. 1). During a well-attended webinar hosted by the *Safety Pharmacology Society* on July 13, 2023, 73°% of respondents supported the need to revise the ICH S7A guideline. 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* symposium held on November 21, 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. Updating ICH S7A would require initiating the ICH process, beginning with the development of a concept paper (see link: ICH Official web site). We believe that outlining key

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Abbreviations

AEs	Adverse Events
EC	European Commission
ECG	Electrocardiogram
EEG	Electroencephalogram
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
EMG	Electromyogram
FDA	Food and Drug Administration
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IWG	Implementation Working Group
NAMs	New Approach Methodologies
NOAEL	No Observed Adverse Effect Level
OECD	Organisation for Economic Cooperation and Development
PhRMA	Pharmaceutical Research and Manufacturers of America
PK/PD	Pharmacokinetic / pharmacodynamic
Q&As	Questions and Answers
QT	Duration of the time between the beginning of the QRS complex and end of the T wave of the electrocardiogram
TK/TD	Toxicokinetic / toxicodynamic
3Rs	Replacement Reduction and Refinement

points to consider for a concept paper will help catalyse broader consultation and engagement with stakeholders, practitioners, and regulators. In this article, we briefly summarize the rationale for revising ICH S7A, as detailed in Valentin and Leishman (2023), while consolidating feedback received since its publication. We explore options for evolving the guideline, highlight essential components to address in a revision, and conclude with actionable next steps.

2. Rationale to evolve ICH S7A

The ICH S7A guideline on safety pharmacology studies, released in 2000, has largely achieved its primary objective *"to help protect clinical trial participants and patients receiving marketed products from potential adverse effects of pharmaceuticals"* (ICH, 2000; Valentin et al., 2023; Valentin and Leishman, 2023). While Phase I clinical trials are generally safe, the frequency and severity of adverse drug reactions, as well as safety-related attrition and product withdrawals, remain significant during late-stage clinical development and post-approval (Cook et al., 2014; Waring et al., 2015; Weaver and Valentin, 2019; Valentin and Redfern, 2017). A proportion of these issues can be attributed, at least in part, to gaps in safety and secondary pharmacology assessments (Weaver and Valentin, 2019). For example, some recent tragic events in Phase I clinical trials have been linked to functional mechanisms—such as cytokine storms, central nervous system symptoms, and suicide—-which fall within the scope of safety and secondary pharmacology (Anon, 2019; Kaur et al., 2018). Furthermore, animal studies have demonstrated the ability to detect small yet sustained increases in blood pressure associated with drugs later linked to adverse cardiovascular effects (e.g., rofecoxib, sibutramine, torcetrapib, celecoxib; Meyer et al., 2015; Yun et al., 2015; Muscara et al., 2000; Hocherl et al., 2002). Furthermore, the acute blood pressure effects of torcetrapib and sibutramine would have been evident in the safety pharmacology studies conducted prior to man. This is consistent with the observation that a substantial proportion of the safety-based attrition was not related to an absence of a nonclinical signal but more a failure of risk management (Cook et al., 2014). Integrated risk assessment schemes, such as those implemented in the ICH E14-S7B Q&As have sought to place nonclinical findings in context and facilitate their use in predicting effects in patients (ICH, 2022a). Given the substantial scientific and technological advancements in drug safety science, the paradigm shift in drug discovery and development, and the continuously evolving regulatory landscape, there is a compelling need to revisit, adapt, and advance the ICH S7A guideline. This evolution could provide opportunities to: i) select and progress optimized drug candidates with greater confidence in their success; ii) refine and adapt clinical monitoring throughout all stages of development, thereby enhancing benefit-risk

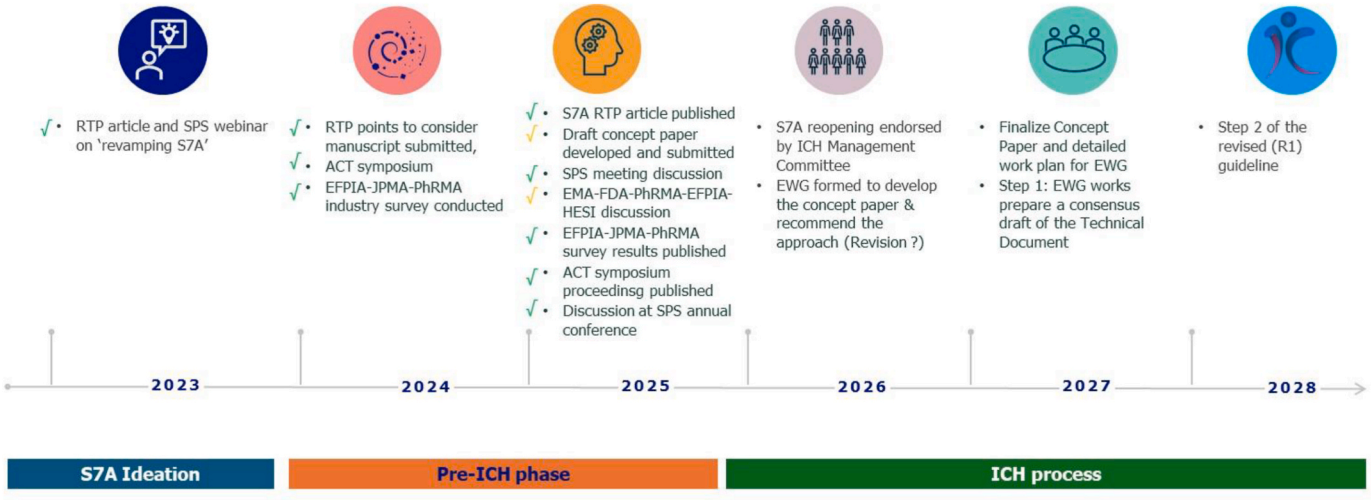

Fig. 1. Anticipated timeframe proposal for activities foresee to re-open and revise ICH S7A. Three phases are anticipated covering an ideation step, a pre-ICH phase leading into the formal ICH process. List of abbreviations used in the figure: ACT, American College of Toxicology; EFPIA European Federation of Pharmaceutical Industries and Associations; EMA, European Medicines Agency; EWG, Expert Working Group; FDA Food and Drug Administration; HESI, Health and Environmental Sciences Institute; ICH, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; PhRMA Pharmaceutical Research and Manufacturers of America; R, Revision; RTP, Regulatory Toxicology & Pharmacology; SPS, Safety Pharmacology Society. The green tick (✓) indicates that activities have been completed or are on track for timely delivery. The amber tick (✓) signifies that activities are at risk of not being delivered on time. Activities that are not preceded by a tick have not yet been started. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

assessments; iii) increase the likelihood of regulatory acceptance while facilitating expedited and streamlined drug discovery and development to benefit patients; iv) reduce unnecessary animal use in safety studies and promote alternative approaches in line with the 3Rs principles (Valentin and Leishman, 2023). The last 25 years have witnessed the development and partial implementation of novel technological platforms spanning *in silico*, *in vitro*, and *in vivo* methodologies (Weaver and Valentin, 2019; Valentin et al., 2023; Pognan et al., 2023; Brennan et al., 2024). These innovations enhance our ability to detect, quantify, and address hazards, thereby optimizing human risk assessment. Societal awareness and regulatory expectations, such as those reflected in the European Commission (EC) Directive guidelines (EC, 2010; EMA, 2024) and the FDA Modernization Act 2.0 (Adashi et al., 2023; Zushin et al., 2023), further emphasize the urgency of applying alternative approaches and advancing animal welfare practices. The drug discovery and development paradigm has evolved significantly, marked by an increasing number and diversity of drugs entering clinical development and of approved drugs—a trend likely to persist given the industry's evolving portfolios (Blanco and Gardinier, 2020; Mullard, 2024; Vargas et al., 2023). Emerging drug modalities, captured in Fig. 2, have matured, achieving clinical success and regulatory approval; these modalities are now routinely integrated into early target appraisals (Blanco and Gardinier, 2020, Fig. 2). However, these innovative approaches pose unique challenges and opportunities for safety and secondary pharmacology assessments, warranting a strategic re-evaluation of the current guidance. Despite these substantial advancements, the ICH S7A guideline has remained unchanged for nearly 25 years—a stark contrast to other ICH safety guidelines, which have been revisited and updated within a few years of their adoption (see Valentin and Leishman, 2023 for details). Many subsequent guidelines, such as ICH S6, S9, and M3 and current draft guidelines such as that addressing oligonucleotide-based therapeutics intersect with or reference secondary pharmacology, highlighting the need for alignment and integration despite a dedicated guideline on this important aspect of pharmaceutical drug safety assessment (see Table 1 for more details). In addition, draft guidelines, such as those on blood pressure and suicidality (FDA, 2022a; FDA, 2022b) have emerged addressing behavioural or physiological endpoints with no reference to safety and/or secondary pharmacology endpoints. These developments further underscore the need for a modernized S7A guideline that harmonizes these interdependencies while addressing the demands of an increasingly diverse and innovative drug development landscape.

3. Integration of ICH S7A and S7B into a unified S7 guideline

The ICH S7B guideline (ICH, 2005), which focuses on evaluating QT/QTc interval prolongation and proarrhythmic potential, represents a clear subset of safety and secondary pharmacology studies. Released five years after ICH S7A, it reflects the significant time required to achieve consensus on the methodologies and approaches necessary to address risks related to repolarization-associated ventricular tachyarrhythmia. Although introduced after S7A, the S7B has already undergone a clarification process via a Q&As procedure (ICH, 2022a). Feedback on Stage 1 of the Q&As highlighted challenges, particularly regarding the document's high level of technical detail. This raised questions about whether some aspects could have been better addressed through alternative frameworks, such as OECD guidance (as was the case for ICH S2; ICH, 2011a) or peer-reviewed publications. The stage 2 of the Q&A process, currently underway, aims to address several critical points: expanding the scope of the guidance beyond new chemical entities,

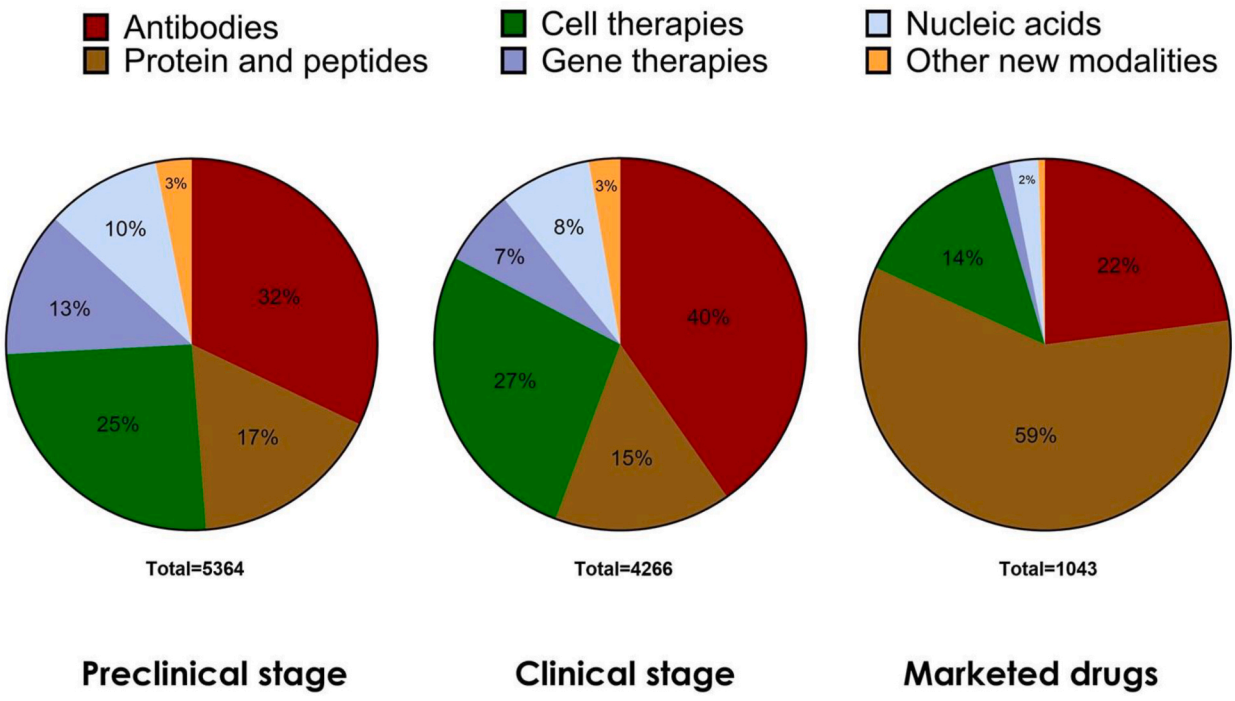

Fig. 2. Distribution of industry portfolios amongst the six categories of "new" modalities and across all phases of the pharmaceutical life cycle. Traditional small molecule portfolio is not captured but is assumed to represent approximately 40°% of the clinical stage portfolio. The antibodies category includes monoclonal, bispecific and antibody drug conjugate. Beyond traditional cell therapies that category includes chimeric antigen receptor-T, stem cells, T-cell receptor therapy, chimeric antigen receptor-transduced and tumor infiltrating lymphocytes. The gene therapies category includes both gene editing and gene augmentation. The nucleic acids category includes DNA and RNA therapies, RNAi and mRNA. The "other modalities" category includes viruses that target and lyse cancer cells, treatment by restoring healthy gut microbia and targeted protein degradation via ubiquitylation. The figure has been adapted and developed from exhibit 3 in (Chen et al., 2024. The, 2024 New Drug Modalities Report | BCG). The data source is from Evaluate Pharma; Boston Consulting Group analysis. The authors are grateful to Mike Brochu, Brian Bush, Dr Lu Chen, and Dr Gian King from the Boston Consulting Group for providing the data necessarily to construct the figure and reviewing the manuscript and to Emma Pawluk from UCB for preparing the Figure.

Table 1
List of nonclinical safety related guidelines referring to secondary pharmacology. Some of them do provide a list of molecular targets to evaluate (e.g., ICH S7B; Drug abuse) whereas some don't. All the ICH guidelines can be access on the ICH official website *(*ICH Official web site: ICH*)*. The drug abuse guideline can be accessed on the FDA website (FDA, 2017. Assessment of Abuse Potential of Drugs | FDA*)*. The authors are grateful to Drs Lyn Rosenbrier-Ribeiro from Grünenthal, and Friedemann Schmidt from Sanofi for developing the Table.

Guideline	Scope	Section	Details
ICH S1	**Carcinogenicity**	2.1: Factors to Consider for a WoE Assessment	… results from secondary pharmacology screens for the parent compound and major metabolites that inform selectivity and off-target potential, especially those that inform carcinogenic risk (e.g. binding to nuclear receptors)
ICH S2	**Genotoxicity**		Consideration of the pharmacological profile for risk assessment
ICH S5	**Reprotoxicology**	4.2: Strategies to address EFD	EFD studies should be conducted in two species to detect the adversity of off-target effects or secondary pharmacology
ICH S7A	**Safety Pharmacology**	2.2 General Considerations in Selection & Design of Safety Pharmacology Studies 2.3.2 Use of In Vivo and In Vitro Studies	Ligand binding or enzyme assay data suggesting a potential for adverse effects … *in vitro* systems can include, but are not limited to: isolated organs and tissues, cell cultures, cellular fragments, subcellular organelles, receptors, ion channels, transporters and enzymes.
ICH S7B Q&As	**Delayed Ventricular repolarization (QT interval prolongation)**	2.3.1 In Vitro IKr Assay 3.1.2 In Vitro Electrophysiology Studies	An *in vitro* IKr assay evaluates the effects on the ionic current through a native or expressed IKr channel protein, such as that encoded by hERG … patch clamp experiments on cells overexpressing cardiac ion channels, including hERG, CaV1.2, and NaV1.5, should be performed …
ICH S8	**Immunotoxicity**		Consideration of the pharmacological profile for risk assessment
ICH S9	**Anti-cancer Pharmaceuticals**	2.1: Studies to support non-clinical evaluation	… secondary pharmacodynamic properties of a pharmaceutical … might be investigated as appropriate
ICH S11	**Paediatric safety**	2.3.2: Pharmacological properties (WoE Factors)	Primary or secondary pharmacological properties of a pharmaceutical can be responsible for unwanted side effects. This can raise concerns for paediatric use …
ICH M3	**Non-clinical safety**	Tble 3	In vitro target/receptor profiling should be conducted.
FDA: Assessment of Abuse Potential of Drugs	**Drug abuse**	B. Screening with Receptor-Ligand Binding Studies	Although a CNS-active drug may have a single high-affinity site, it is often the case that drugs have multiple mechanisms of action with varying degrees of affinity. Some examples of neuronal systems related to abuse potential that should be assayed include the following: • Dopamine, • Serotonin, • Gamma-aminobutyric acid (GABA), • Opioid, • Cannabinoid, • N-methyl-D-aspartate (NMDA), • Ion-channel complexes (e.g., calcium, potassium, chloride), • Transporters (e.g., dopamine, serotonin, GABA)

leveraging toxicology study data to inform an integrated ICH E14/S7B risk assessment, and developing a framework for assessing QTc prolongation and proarrhythmia risks for novel modalities. The completion of stage 2, anticipated by the end of 2025, presents an opportunity to consolidate the outcomes of the ICH S7A review, the ICH S7B guideline, and their associated Q&As into a comprehensive, overarching ICH S7 guideline encompassing all key aspects of safety and secondary pharmacology. Although integrating the S7A, S7B, and associated Q&As into a single guidance could streamline instructions, enhance usability, and align regulatory expectations across the pharmaceutical industry, the challenges related to the practicality and feasibility of such consolidation—especially considering its interdependencies with other guidance, such as E14—may need to be addressed separately at a later stage.

4. Options for evolving an ICH guidance

The ICH follows four main procedures for harmonisation activities: **Formal ICH Procedure**, **Q&A Procedure**, **Revision Procedure**, and **Maintenance Procedure** (see link: ICH Official web site). Each activity begins with a **concept paper**, which provides a brief overview of the proposed changes. The **formal ICH procedure** applies to the development of new ICH guidelines and is not relevant in this context. Similarly, the **maintenance procedure** is used to update a guideline when new information is available or when content is outdated, which is not the case for ICH S7A. The **Q&A procedure** is used when further clarification is needed to aid the interpretation and consistent implementation of existing ICH guidelines. This process begins when stakeholders raise questions or issues that highlight the need for additional guidance. These questions are then formulated into a model Q&A, with standard responses developed. The Q&A procedure is typically quicker, offering a more immediate clarification without revising the guideline itself. The **revision procedure** is employed when existing guidelines need to be updated due to scientific advancements or when new information must be incorporated. This procedure follows a similar process to the formal ICH procedure, with five steps, but results in a revised guideline, designated with an "R". This approach is more comprehensive and can result in a more substantial revision of the guideline, rather than simply providing clarifying information. For ICH S7A, although both the **Q&A** and **revision** procedures are viable options considering the broad scope of issues identified through ongoing discussions, a **revision procedure** may be more appropriate in addressing the emerging complexities. Regardless of the chosen procedure, the initial step is the development of a concept paper. Given that revisions can be time-consuming, alternative approaches should be explored to streamline the ICH process and shorten timelines.

5. Points to consider for revising the ICH S7A

Six main pillars described below have been identified for consideration to evolve ICH S7A.

5.1. Clarification of adversity in safety pharmacology studies

Although the term *adverse* appears 26 times in the ICH S7A guideline, it is never formally defined (ICH, 2000). A recent expert review highlighted the absence of a formal definition for adversity in safety pharmacology and the lack of guidance on determining the No Observed Adverse Effect Level (NOAEL), a critical parameter in safety evaluation. The review also noted that defining a NOAEL is not mandatory for advancing investigational drugs through regulatory processes. Consequently, the binary classification of findings as either "toxic" or "non-toxic" lacks nuance, ignoring the context and severity of observed pharmacodynamic effects (Mow et al., 2020). Experts have

recommended avoiding rigid definitions of *adversity* and NOAEL in safety pharmacology studies. Instead, describing test article-related pharmacodynamic effects with reasoned arguments as part of an integrated risk assessment could provide regulators and clinical pharmacologists with a more transparent and comprehensive understanding of relevant findings at each dose or exposure level. Furthermore, allowing flexibility in characterizing adverse effects may better align with the diverse endpoints assessed in safety pharmacology, which often span a continuum of functional changes. Future revisions to ICH S7A should aim to incorporate these considerations, promoting a more context-specific and nuanced framework for evaluating adversity.

5.2. Considerations for human-based in vitro and in silico secondary pharmacology test systems

Secondary pharmacology screening for undesirable off-target activities is now standard practice in drug development, with regulatory agencies increasingly requesting data on interactions with targets associated with known side effects (Brennan et al., 2024; Papoian et al., 2015; Jenkinson et al., 2020). Current safety guidelines refer to secondary pharmacology but differ significantly in specifying molecular targets, ranging from absent to highly prescriptive requirements (Table 1). Recent discussions, and publications have emphasized the need for optimizing secondary pharmacology assessments through best practices, to expand safety-associated target panels, and to improve interpretation, contextualization of off-target activities and regulatory submission (Brennan et al., 2024; Papoian et al., 2015; Jenkinson et al., 2020; Dodson et al., 2021). A more comprehensive and rigorous secondary pharmacology profiling of drug candidates may enable the identification of potential off-target-related side effects, warranting further nonclinical and/or clinical investigations or monitoring. Importantly, secondary pharmacology extends beyond small molecules to all other modalities. For example, monoclonal antibody selectivity is assessed using cell microarrays and tissue cross-reactivity assays, while antisense oligonucleotides therapeutics require hybridization-dependent and independent *in silico* and *in vitro* methods (Goyenvalle et al., 2023; ICH, 2024; Norden et al., 2024; MacLachlan et al., 2021; Vicart et al., 2025). Furthermore, incorporating New Approach Methodologies (NAMs) into regulatory submissions is an additional area for growth (Stresser et al., 2024; Avila et al., 2020; Pognan et al., 2023), enabling more predictive and human-relevant safety assessments. NAMs, including computational models and advanced *in vitro* systems, hold promise for refining safety evaluations, reducing reliance on animal models, and addressing limitations associated with traditional safety pharmacology approaches. Revisions to ICH S7A could provide greater clarity on the integration of these novel systems and establish standardized frameworks for their use in regulatory submissions.

5.3. Functional endpoint assessment using in vivo state-of-the-art platforms

While non-animal approaches should be encouraged, *in vivo* studies remain essential for safety pharmacology (ICH, 2000; Harrell et al., 2024; Valentin et al., 2023). Safety pharmacology endpoints (e.g., ECG, EEG, EMG, arterial, venous and cardiac pressures, blood gases) can often be measured in both animals and humans using similar technologies, enhancing cross-species translation and contextualization of findings (Ewart et al., 2014; Park et al., 2018; Friedrichs et al., 2024; Valentin et al., 2023). The ICH S7A guideline could evolve to emphasize critical biological and physiological parameters, leaving room for sponsors to adopt emerging techniques. Continuous technological advancements, such as telemetry and non-invasive imaging, enable the collection of high-quality data while minimizing animal use and improving animal welfare. Any model or assay must demonstrate human biological relevance, technical robustness, and sensitivity to detect human-relevant effects (Valentin et al., 2009; Trepakova et al., 2009). Retrospective analyses of *in vivo* safety pharmacology test systems across various organ functions have demonstrated variable predictive capacity in detecting human-relevant effects, which may be attributed to several, potentially addressable, factors (Ewart et al., 2014; Park et al., 2018; Friedrichs et al., 2024; Mead et al., 2016). Some studies have also highlighted the limited added value of certain safety pharmacology assessments (Guth and Pugsley, 2017; Baldrick, 2021), reinforcing the need for a revision of ICH S7A. Integrating multiple organ-specific endpoints within the same study, including toxicology assessments, would allow for longitudinal evaluations over weeks or months following chronic dosing. This approach enhances efficiency while aligning with the 3Rs principles (Harrell et al., 2024) and could be particularly relevant for assessing cardiovascular, respiratory, and nervous system functions. The inclusion of composite endpoints—such as combined cardiovascular, neurological, and respiratory measures—leveraging highly sensitive, state-of-the-art, and human-relevant technologies may offer a more comprehensive assessment of a drug's safety profile (Valentin and Leishman, 2023). Furthermore, the incorporation of state-of-the-art analytical tools, such as artificial intelligence and machine learning, can enhance the interpretation of complex datasets, facilitating more informed decision-making during drug development.

5.4. Principles for validation and qualification of novel models and assays

To support regulatory decision-making, it is essential to clarify the distinction between models and assays. Models represent simplified systems for understanding and prediction, while assays measure specific biological activities. Both are vital in safety and secondary pharmacology. These fields have pioneered novel *in silico*, *in vitro*, and *in vivo* models and assays, some of which are now part of regulatory frameworks (e.g., ICH S7B, E14/S7B Q&As; ICH, 2005; ICH, 2022a). In retrospect, the now common *in vitro* hERG functional assay is a good example of a NAM when it was introduced to identify new chemical entities with proarrhythmia risk (ICH, 2005; Rampe and Brown, 2013). The scientific evolution and practical implementation of the hERG assay is an excellent example of the value of non-clinical data and could guide the implementation of new assays. Future updates to ICH S7A should outline general principles for validating and qualifying models and assays to expedite their adoption in regulatory contexts; to that end, some precedents do already exist in regulatory guidelines (see Appendix 2 in ICH S5(R3); ICH, 2020). However, care must be taken to balance validation requirements with the need to encourage innovation, ensuring that regulatory expectations do not hinder the application of emerging technologies. Establishing tiered validation frameworks, wherein the level of validation required is proportional to the intended use of the model or assay, may strike an optimal balance. For instance, exploratory models used in early drug development may not require the same degree of validation as those intended for pivotal regulatory decisions. One could argue that the Comprehensive In vitro Proarrhythmia Assay (CiPA) framework was an example of an impactful tiered approach (Wallis et al., 2018). Additionally, fostering collaboration between pharmaceutical industry, academia, service providers, technology developers and regulatory agencies could accelerate the development of consensus standards, enabling more rapid incorporation of novel tools into safety pharmacology paradigms. Experience gathered in the first 15 years after implementation of ICH S7A highlighted that these regulatory studies had limited additional value beyond the candidate selection work already conducted (Guth and Pugsley, 2017). This likely reflected the need of sponsors to detect effects as early as possible to streamline early discovery and development. The earlier tests conducted during candidate selection may fit the definition of novel models and assays currently being used. Individual sponsors then have qualified these assays to a level sufficient in the context of internal decisions. If an appropriate level of qualification could be achieved for a regulatory context these models or assays could be used in place of the current regulatory studies with low perceived added value.

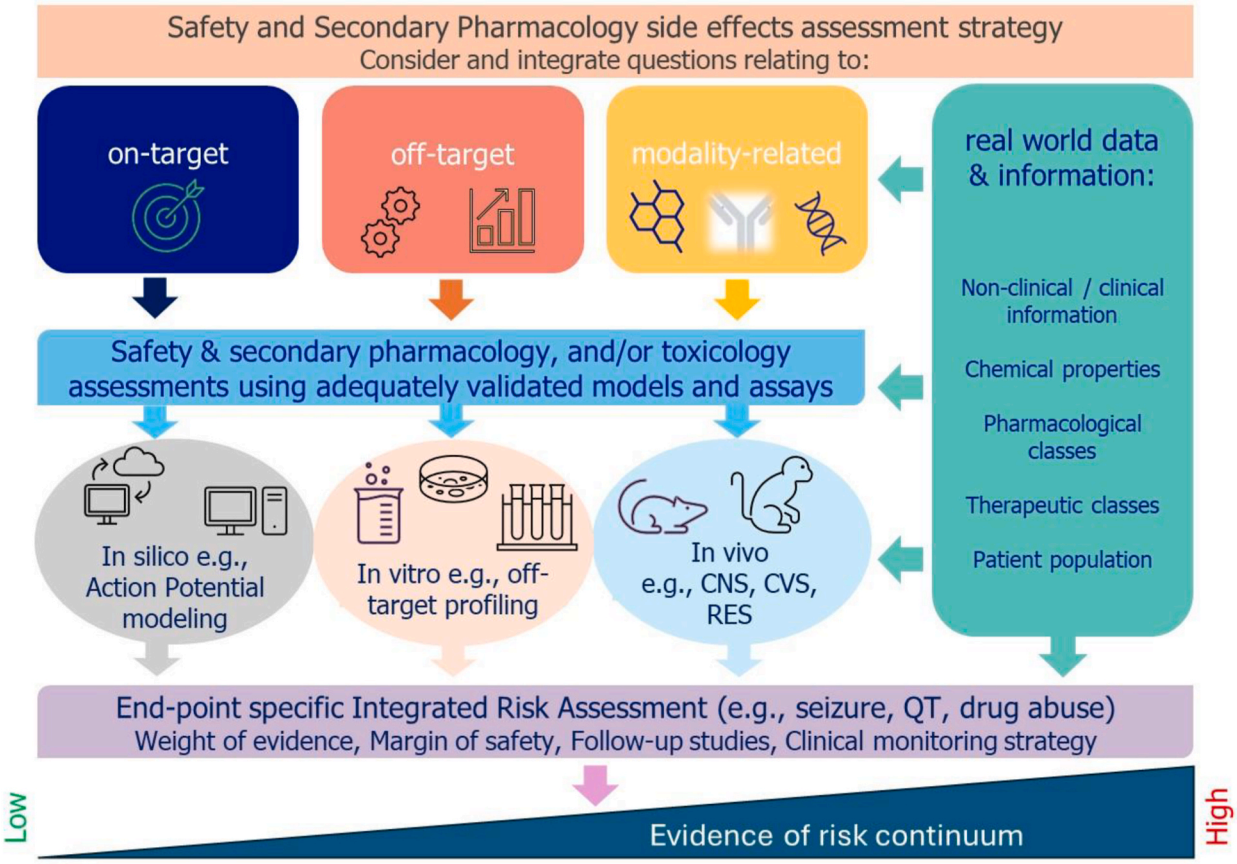

Fig. 3. Framework proposal to guide the safety and secondary pharmacology assessment of pharmaceutical products irrespective of the therapeutic modality. It results from an evolution of the framework described in the ICH S7B (ICH, 2005) and its subsequent evolution via the Q&As (ICH, 2022a). Five of the six main pillars that have been identified for consideration to evolve ICH S7A are presented in the figure. An ICH S7A revision should aim to address key aspects of safety and secondary pharmacology, including the definition of adversity (not-captured on the schematic), the integration of human-relevant *in vitro* and *in silico* models, and the adoption of state-of-the-art *in vivo* platforms using robust, adequately validated models and assays. Further considerations should include the development of principles for model and assay validation, the promotion of integrated non-clinical/clinical risk assessment frameworks, and incorporation of weight of evidence approaches. Revised guidelines would also emphasize sustainable practices by adapting to evolving therapeutic modalities, while reducing reliance on animal testing through New Approach Methodologies. The revision seeks to enhance the benefit-risk evaluation of drug candidates, refine clinical monitoring, foster regulatory acceptance, and streamline drug development. CNS, Central Nervous System; CVS, Cardiovascular System; RES, Respiratory System.

5.5. *A modality-agnostic, sustainable guideline*

The ICH S7A guidelines primarily focus on traditional NCEs, with limited references to conditions under which safety pharmacology studies may not be necessary, such as for locally applied agents or biotechnology-derived products that achieve highly specific receptor targeting (ICH, 2000). As shown in Fig. 2, the rapid emergence of novel modalities—such as monoclonal antibodies, RNA therapeutics, and gene therapies—offers significant therapeutic potential but presents unique safety assessment challenges (Blanco and Gardinier, 2020; ICH, 2011b; FDA, 2024). To ensure the long-term relevance of ICH S7A, a modality-agnostic framework is needed—one that can adapt to emerging modalities while maintaining robust safety standards. Establishing such a framework would help ensure that the guideline remains applicable and sustainable over time. Key considerations should include the potential for modality-driven on-target or off-target side effects, target tissue distribution, selectivity of the therapeutic agent, and its exposure in various body compartments. Addressing these questions can help design optimal safety and secondary pharmacology evaluation packages and provide a sustainable framework for evolving regulatory requirements (Fig. 3). Incorporating principles of flexibility and adaptability into the guideline will be critical to accommodate the dynamic landscape of therapeutic innovation. For example, the guideline could include decision trees or modular approaches to tailor safety assessments based on the unique characteristics of each modality. A graphical representation of such a framework already appeared in ICH S7B; in Fig. 3 all the elements of that ICH S7B-specific example are represented. Emphasizing scientific principles over prescriptive requirements will also ensure the guideline remains relevant as new therapeutic classes emerge. An updated guideline should allow drug sponsors to incorporate new data or assays into regulatory submissions, promoting more relevant and advanced safety and secondary pharmacology science that better reflects human relevance.

5.6. *Integrated risk assessment, weight of evidence and margin of safety*

Integrated risk assessment spans the continuum from preclinical development to post-approval, informing clinical study designs and interpretation of results. This concept, central to ICH guidelines (e.g., ICH, 2016; ICH, 2005; ICH, 2022b), integrates pharmacodynamic findings (e.g., dose/exposure dependency, reversibility, human relevance) with PK/PD relationships to establish a margin of safety based on the totality of evidence and, ultimately, a benefit-risk assessment. The principles outlined in ICH S7B and subsequent Q&As (ICH, 2005; Anon., 2022) could be extended to all core and supplemental physiological systems covered by ICH S7A, ensuring consistency and relevance across therapeutic modalities (Fig. 3). The integrated risk assessment framework should also encompass emerging endpoints and technologies,

incorporating data from NAMs, advanced *in vitro* systems, and *in silico* modeling. Additionally, incorporating real-world evidence from post-market surveillance could strengthen the translational relevance of preclinical findings, bridging the gap between nonclinical studies and clinical outcomes. Revisions to ICH S7A should emphasize the iterative nature of risk assessment, encouraging sponsors to refine their safety evaluations as new data becomes available throughout the drug development lifecycle; this was the case with the assessment of QT/proarrhythmic risk (Rampe and Brown, 2013; Wallis et al., 2018; Vargas et al., 2023) and other target organ functions (Ewart et al., 2014; Park et al., 2018; Friedrichs et al., 2024; Mead et al., 2016).

6. Recommendations and next steps

Twenty-five years after its release, we recommend revising and consolidating the ICH S7A and S7B guidelines into a unified S7 guideline via a revision procedure (Figs. 1 and 3). This revision should reflect the latest scientific advancements, technological innovations, and the ever-evolving pharmaceutical and regulatory landscapes. Guidelines should evolve from rigid prescriptions to a "menu of options" that encourage innovative, data-driven approaches in safety science, rather than stifling new thinking with outdated requirements. The six pillars outlined in this article could serve as a foundation for drafting a formal ICH concept paper. A revamped S7A guideline has the potential to facilitate the selection and advancement of optimized drug candidates, refine and adapt clinical monitoring strategies, enhance the likelihood of regulatory acceptance, reduce unnecessary animal use by promoting alternative methodologies, and to streamline the overall drug development process. By addressing these priorities, the revised guideline could significantly improve the efficiency and ethical standards of nonclinical and clinical drug safety assessments.

CRediT authorship contribution statement

Jean-Pierre Valentin: Writing – review & editing, Writing – original draft, Conceptualization. **Derek Leishman:** Writing – review & editing, Writing – original draft, Conceptualization.

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Declaration of competing interest

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Data availability

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

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