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2000–2023 over two decades of ICH S7A: has the time come for a revamp?

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ABSTRACT

The ICH S7A guideline on safety pharmacology studies released over 20 years ago largely achieved its objective "*to help protect clinical trial participants and patients receiving marketed products from potential adverse effects of pharmaceuticals*". Although, Phase I clinical trials are generally very safe, the incidence and severity of adverse events, the safety related attrition and product withdrawal remain elevated during late-stage clinical development and post approval, a proportion of which can be attributed at least in part to safety pharmacology related issues. Considering the latest scientific and technological advancements in drug safety science, the paradigm shift of the drug discovery and development process and the continuously evolving regulatory landscape, we recommend revisiting, adapting and evolving the ICH S7A guideline. This might offer opportunities i) to select and progress optimized drugs with increased confidence in success, ii) to refine and adapt the clinical monitoring at all stages of clinical development resulting in an optimized benefit/risk assessment, iii) to increase likelihood of regulatory acceptance in a way compatible with an expedited and streamlined drug discovery and development process to benefit patients and iv) to avoid the unnecessary use of animals in 'tick-the-box' studies and encourage alternative approaches. As presented in the article, several options could be envisioned to revisit and adapt the ICH S7A taking into consideration several key features.

1. Problem statement

The ICH S7A guideline on safety pharmacology studies for human pharmaceuticals[1] released over 20 years ago "*was developed to help protect clinical trial participants and patients receiving marketed products from potential adverse effects of pharmaceuticals*"; from that standpoint it largely achieved its objective (Anon, 2001; Valentin and Hammond, 2008). Phase I clinical trials are generally very safe, although three unfortunate tragic events were reported over that period of time (Anon, 2019; Kaur et al., 2018). Those serious (i.e., fatal) adverse events (AEs) were functional in nature (i.e., cytokine storm, central nervous system symptoms, and suicide) and therefore falling under the broad remit of safety and/or secondary pharmacology. However, the incidence and severity of AEs, the safety related attrition and product withdrawal remain elevated during late-stage clinical development and post approval; a proportion of those AEs can be attributed at least in part to safety pharmacology related issues (Valentin and Redfern, 2017; Weaver and Valentin, 2019). Moreover, over the last 2 decades, there has been i) significant scientific and technological advancements in drug safety science, ii) a paradigm shift in the drug discovery and development process and iii) a continuously evolving regulatory landscape; all of which are presented and discussed in this article. When looking at the temporal evolution of ICH safety-related guidelines, and in contrast to the ICH S7A, most undergo an initial revision within 2 decades (Table 1), suggesting that the S7A has either been fully successful, or largely ignored and thus not requiring any updating. We therefore asked whether revisiting, adapting, and evolving the ICH S7A guideline might offer opportunities to select and progress optimized drugs with increased confidence in success, to refine and adapt the clinical monitoring at all stages of clinical development resulting in an optimized benefit/risk assessment and to increase likelihood of regulatory

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[1] During the drug discovery process, 3 types of pharmacology studies are conducted; primary, secondary and safety pharmacology studies. Primary pharmacodynamic studies aim at investigating the mode of action and/or effects of a substance in relation to its desired therapeutic target. Secondary pharmacodynamic studies aimed at investigating the mode of action and/or effects of a substance not related to its desired therapeutic target, whereas safety pharmacology studies aimed at investigating the potential undesirable pharmacodynamic effects of a substance on physiological functions in relation to exposure in the therapeutic range and above. Safety pharmacodynamic effects may result from activity at the primary molecular target, secondary targets, or non-specific interactions (Anon, 2001; Valentin and Hammond, 2008).

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List of abbreviations:

AEs	Adverse Events
CiPA	Comprehensive *in vitro* proarrhythmia assay
CROs	Contract Research Organizations
CTA	Clinical Trial Application
ECG	electrocardiogram
EEG	electroencephalogram
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMG	electromyogram
FDA	Food and Drug Administration
FIHT	First In Humans Trial
GLP	Good Laboratory Practice
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IND	Investigational New Drug
IWG	Implementation Working Group
NOAEL	No Observed Adverse Effect Level
NOEL	No Observed Effect Level
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
QTc	heart rate corrected duration of he QT interval
TdP	Torsades de Pointes
TQ	Tthorough QT study
TK/TD	toxicokinetic/toxicodynamic
3Rs	Replacement, Reduction and Refinement

Table 1
Temporal evolution for revision of ICH safety-related guidances in relation to their initial year of finalization (step 4).

Guidelines	Topic	Year of finalization (Step 4)	Year of revision (Step 4)
S5	Reproductive Toxicology	1993	1995 S5(R1); 2000 (S5R2); 2020 S5(R3)
S3	Toxicokinetics and Pharmacokinetics	1994 (S3A and S3B)	2017 (S3A Q&As)
S1	Carcinogenicity Studies	1995 (S1A); 1997 (S1B); 1997 (S1C)	2005 (S1C(R1)); 2008 (S1C(R2)); 2022 (S1B (R1))
S2	Genotoxicity Studies	1995 (S2A); 1997 (S2B)	2011 S2(R1)
S6	Biotechnology Products	1997	2111 S6(R1)
M3	Nonclinical Safety Studies	1997	2006 (M3(R1)); 2009 (M3(R2); 2011 (M3 (R2) Q&As (R2))
S4	Toxicity Testing*	1998	*define the duration of chronic toxicity in rodents and non-rodents (6- and 9-months duration, respectively)
S7A	Safety Pharmacology Studies	2000	
S7B	Nonclinical Evaluation of QT	2005	2022 (E14/S7B Q&As)
E14	Clinical Evaluation of QT	2005	2008 (E14 Q&As); 2012 (E14 Q&As (R1)); 2014 (E14 Q&As (R2)); 2015 (E14 Q&As (R3)); 2022 (E14/S7B Q&As)
S8	Immunotoxicology Studies	2005	
S9	Nonclinical Evaluation for Anticancer Pharmaceuticals	2009	2019 (S9 Q&As)
S10	Photosafety Evaluation	2013	
S11	Nonclinical Paediatric Safety	2020	

Most safety related guidelines are typically updated via a revision and/or Q&As process within 2 decades from their initial finalization date. Data extracted from: https://www.ich.org/page/safety-guidelines. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use.

acceptance in a way compatible with an expedited and streamlined drug discovery and development process to benefit patients.

2. Regulatory landscape

A review conducted 5 years after the ICH S7A implementation already identified gaps and challenges associated with the guideline, most of which do persist nowadays (Valentin et al., 2005); for example the need for further refinement or clarification such as the specifics of study design including the selection of dose/concentration, choice of species, modeling of the temporal pharmacodynamic (PD) changes in relation to pharmacokinetic (PK) profile of parent drug and major (human) metabolites, use of an appropriate sample size, use of positive controls, standardization of assays, statistical power analysis as a means of demonstrating the sensitivity of the test system, testing of human-specific metabolites and demonstrating not only the model's sensitivity and reproducibility, but also its specificity for predicting AEs in humans. Those gaps might have created uncertainty in the confidence of some models (e.g., *in vivo* rodent CNS or respiratory assessment assays; Mead et al., 2016; Paglialunga et al., 2019) or endpoint assessments (e.g., arterial blood pressure; Ewart et al., 2014) and might have affected the willingness to use such data for regulatory decision making. There was also discussion of when these studies are needed in relation to the clinical development plan and how those studies would influence the integrated risk assessment during the later stages of clinical development or once drugs have been introduced to the marketplace (Valentin et al., 2005). In addition, clarification remains to be provided on how to interpret, contextualize and build an integrated risk assessment based on safety pharmacology data; for example, although the term '*adverse*' is used numerous times in the guideline, no definition is provided, and no consensus exists within the scientific community on how to define and use *adversity* in a safety pharmacology context. Similarly, there is no consensus on defining and using the NOAEL and NOEL in the context of safety pharmacology studies (Baird et al., 2019; Mow et al., 2020). Although the guideline encourages a multifaceted approach combining and integrating 'core battery', 'follow-up' and 'supplemental' studies, it seems that such approaches are unfrequently used. To the best of our knowledge, there has been little or no FIHTs submission (i.e., IND, CTA) refuted or significantly delayed based on suboptimal safety pharmacology datasets; on the contrary there is evidence of drugs progressing through to clinical trials despite incomplete or suboptimal safety pharmacology dataset (Park et al., 2018). This raises the question about the appreciation and impact of safety pharmacology data both from a sponsor and a regulatory point of view. Of interest the ICH S7B, released 5 years after the ICH S7A, and focusing on a subset of safety pharmacology studies has undergone a Q&A process (Anon, 2022a) to reflect the latest advances in the scientific, technological, clinical, and

regulatory fields. The objective being to promote greater emphasis and impact of non-clinical data on clinical QTc/TdP assessment by using robust, high quality *in silico*, *in vitro* and *in vivo* non-clinical assays, thus increasing confidence in clinical assets whilst streamlining clinical development. Another critical endpoint in safety pharmacology assessments, blood pressure, is the topic of a draft guidance from FDA and a 'thorough blood pressure study' analogous to a thorough QT (TQT) study is a potential outcome (Anon, 2022b). This would suggest the blood pressure endpoints and other *in vitro* safety pharmacology endpoints in the domain of S7A should be integrated in a way exemplified by the recent ICH S7B Q&As. In contrast to the new S7B Q&As, ICH S7A relies primarily on *in vivo* data with little reference to *in vitro* or *in silico* approaches. This is conflicting with the European Directive 2010/63/EU and subsequent evolutions on the protection of laboratory animals, which makes mandatory the application of the 3R principles (replacement, reduction, refinement) and the use of alternative approaches wherever possible (Anon, 2010b; Anon, 2022g; Anon, 2022h). Moreover, secondary pharmacodynamic studies[1] that are increasingly considered for hazard identification and human risk assessment, management and mitigation and are an integral part of the regulatory submission process alongside primary and safety pharmacology studies, are not associated with dedicated guidelines other than sparse reference in the ICH S7A (Bowes et al., 2012; Anon, 2001; Papoian et al., 2015). However, *in vitro* binding and/or functional human based assays known for their association to safety liabilities are being progressively considered in a regulatory setting (e.g., Comprehensive *in vitro* proarrhythmia assay (CiPA), Suicidal ideation, Drug abuse liability; Anon, 2022a; Anon, 2012a; Anon, 2017a; Jenkinson et al., 2020; Valentin et al., 2018), and regulatory actions taken-up by health authorities (Papoian et al., 2015). Furthermore, subsequent to the ICH S7A implementation, several guidelines have emerged or have been revisited that cross-referenced or showed inter-dependencies with the ICH S7A (e.g., ICH S6, S9, M3R2, FIHT; Anon, 2011; Anon., 2010; Anon, 2009; Anon, 2012b; Anon, 2017b; Anon, 2018) that would deserve further scrutiny. That said the ICH S7A regulatory submission packages are largely unchanged, and if anything, are probably more streamlined compared to what they were when first introduced 20 years ago. Furthermore, the emergence of regulatory science defined as '*the science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of all FDA regulated products*' offers opportunity to facilitate the development of innovative new drugs and optimize use of approved drugs; this being an integral part of the dual mission of several global regulatory agencies to protect and promote public health (Rouse et al., 2018a,b).

3. Scientific and technological environment

The last 2 decades have seen the development and to a certain extent the implementation of novel technological platforms that can further enhance or refine our ability to detect and quantify hazards to optimize the human risk assessment. For example, miniaturized telemetry devices implantable or wearable are now available to continuously record biological parameters from freely moving laboratory animals (e.g., ECG, EEG, EMG, arterial, ventricular, or venous blood pressures, renal and gastrointestinal parameters; Anon, 2022d; Anon, 2022e; Anon, 2022f, Al-Saffar et al., 2015; Benjamin et al., 2015). Complex behavioral patterns can be monitored, analyzed, and interpreted from singly or group housed freely moving animals via cage-built sensors or externally connected monitoring devices (e.g., CRACK-IT; Redfern et al., 2017). Most of those technologies are amenable to acute or chronic settings including long-term toxicity studies. At the other end of the spectrum, there is growing consideration for understanding the molecular mechanisms underpinning safety liabilities (e.g., hERG inhibition and its association to QTc prolongation and TdP; $5HT_{2B}$ receptor agonism and its association to cardiac valvulopathy) for potential implementation in a regulatory context (Anon, 2005; Anon, 2022a; Papoian et al., 2015). There has been tremendous efforts placed in understanding the confidence in experimental models by developing and applying frameworks focusing on i) the confidence in the biology of the test system to mimic human biology and pathophysiology; ii) the technical confidence and robustness in the assay or model (e.g., sensitivity, reproducibility); iii) the confidence in the human relevance or in the translation aspects from *in silico*, *in vitro*, or *in vivo* animal model to human healthy subjects or diseased patient (Valentin et al., 2009; Trepakova et al., 2009). Despite those efforts, 'apparent' gaps remain regarding the human relevance of some of the models (e.g., *in vivo* rodent CNS or respiratory assessment assays; Mead et al., 2016; Paglialunga et al., 2019) or endpoints within a model (e.g., arterial blood pressure; Ewart et al., 2014) currently used under the ICH S7A; raising the question around their value in functional safety assessment in support to FIHTs. Promising and relevant functional or soluble biomarkers (e.g., JTpeak/Tpeak-Tend as biomarker of TdP, miRNA as biomarkers of cardiac or hepatic injuries), and additional relevant parameters (e.g., left ventricular pressure, EEG) are being incorporated as part of the safety pharmacology and/or chronic toxicology evaluation. Over the years questions arose about the value and impact of the assessment of "supplemental" organs systems (e.g., renal, gastrointestinal and immune systems) as well as of respiratory function especially when using sub-optimal, low predictive capacity models. For example, the assessment of lung mechanics (e.g., airway resistance, lung compliance) has been relegated to the rank of "follow-up" investigations and therefore is not required prior to first administration to humans (Anon, 2001; Murphy D.J., 2014). One key aspect to interpreting and contextualizing the safety pharmacology dataset is to establish the PK/PD (or TK/TD) relationship of the test article or its metabolite(s). To this effect approaches are becoming available to monitor PK (or TK) and PD (or TD) concurrently in the same animal (Kamendi et al., 2016; Vargas et al., 2021). There is growing acceptance that PK/PD (or TK/TD) assessment can provide accurate determination of margin of safety thus enabling a more informed decision-making process. Very recently, the passing of the FDA modernization act (Anon., 2022c) "*allows an applicant for market approval for a new drug to use methods other than animal testing to establish the drug's safety and effectiveness. Under this bill, these alternative methods may include cell-based assays, organ chips and micro-physiological systems, sophisticated computer modeling, and other human biology-based test methods*". This point is of critical importance since there is increasing societal awareness and pressure to apply the 3Rs principles of animal welfare (Anon, 2022g) and wherever feasible to reduce the use of animal testing for scientific purposes (see Anon, 2022h).

4. Drug discovery and development paradigm

Over the recent years, there has been an increase in the number and diversity of approved drugs (Mullard, 2022) despite on-going challenges i) to enhance drug candidate quality (including benefit/risk), ii) to accelerate drug development by shortening time to FIHTs and market, and iii) to reduce drug discovery and development cost by increasing effectiveness and efficiency. Since the early 2000s, the concept of early safety-derisking (i.e., safety frontloading; discovery safety) primarily based on *in cerebro*, *in silico* and *in vitro* approaches has been developed and successfully implemented leading to significant reduction of certain liabilities in clinical development (e.g., QTc prolongation/TdP), fewer side effects in the GLP-FIH package safety pharmacology package and increase likelihood of success of drug candidates (Atienzar et al., 2016; Weaver and Valentin, 2019; DaSilva et al., 2020; Beilmann et al., 2019; Roberts et al., 2014). The implementation of ICH S7A resulted in a shift in emphasis and organizational alignment from general pharmacology units in Research Areas to GLP focused safety pharmacology units aligned to non-clinical development or safety assessment functions. More recently a significant shift from studies conducted in-house to studies performed at CROs was noted which is associated with reduced flexibility and innovation despite extended timelines and costs. After the

Fig. 1. Assessment of key safety liabilities across the entire pharmaceutical life cycle by deploying and integrating non-clinical (non-regulated and regulated) and clinical assessments. The examples provided above focus on the assessment of drug-induced QT prolongation and TdP (left) and of drug abuse risk (right). These schematics illustrate the value of a tiered approach to enable hazard identification, risk assessment, management, and mitigation at all stages of the pharmaceutical life cycle.

Table 2
Potential options to revisit the ICH S7A.

Options	Scope of the revised S7A	Examples
Option 1	**Develop a comprehensive S7A encapsulating non-clinical assessment of key safety liabilities in support to all clinical phases alongside clinical guidances**	**Incorporate non-clinical evaluation of QTc/TdP (Anon, 2005; Anon, 2022b), drug abuse (Anon, 2017a), suicidality (Anon, 2012b), seizure (Easter et al., 2009), blood pressure (Anon, 2022a), cardiac inotropic assessments.**
Option 2a	**Revise S7A to support FIHTs, supplemented by independent, stand-alone non-clinical and clinical guidances addressing key safety liabilities**	**Revise S7A (Anon, 2001) and separate ICH S7B and E14 supporting pro- arrhythmia assessment (Anon, 2005a; Anon, 2005b; Anon, 2022b).**
Option 2b	**Revise S7A to support FIHTs, supplemented by multidisciplinary (M) combined non-clinical and clinical guidances addressing key safety liabilities**	**i) Develop a multidisciplinary (M) drug abuse liability guidance based on existing FDA guidance integrating non-clinical and clinical assessments; Anon, 2017a; ii) Collapse S7B and E14 into a M guideline. This may already be the implicit approach given the joint ICHE14/S7B Q&As with their 'integrated risk assessment' focus (Anon, 2022b).**

FIHTs, First In Human (Clinical) Trials.

implementation of ICH S7A a question arose on whether some potentially promising drugs might have been prevented in progressing to FIHT in relation to sub-optimally designed, conducted, analyzed, interpreted or contextualized safety pharmacology data; this question remains largely unanswered. New drug modalities including novel formats of antibodies (e.g., bi and tri-specific, antibody drug conjugates), antisense oligonucleotides, RNA therapeutics, protein degraders, covalent inhibitors, next generation of peptides (e.g., cyclopeptides) and cell and gene therapies have matured, demonstrating clinical success and regulatory approval and are now consistently considered early in target appraisal (Blanco and Gardinier, 2020); these novel approaches offer challenges and opportunities and deserve strategic thinking when considering their safety and secondary pharmacology assessment.

5. Recommendations

Examples on how key safety liabilities (e.g., assessment of QT/TdP and drug abuse risks) are being addressed across the entire pharmaceutical lifecycle are illustrated in Fig. 1 by deploying and integrating non-clinical (regulated and non-regulated) and clinical assessments. Similar approaches could be envisioned to tackle other safety liabilities (e.g., Suicidal ideation, Seizure liability, Blood pressure effects, Inotropic effects; Chappell et al., 2017; Easter et al., 2009; Anon, 2022b; Valentin et al., 2015). Considering the gaps and weaknesses identified in previous sections, and the latest scientific and technological advancements in drug safety science, the paradigm shift in the drug discovery and development process and the continuously evolving regulatory landscape, we recommend revisiting, adapting, and evolving the ICH S7A guideline. This might offer opportunities i) to select and progress optimized drugs with increased confidence in success, ii) to refine and adapt the clinical monitoring at all stages of clinical development resulting in an optimized benefit/risk assessment, iii) to increase likelihood of regulatory acceptance in a way compatible with an expedited and streamlined drug discovery and development process to benefit patients and iv) to avoid the unnecessary use of animals in 'tick-the-box' studies and encourage alternative approaches. As presented in Table 2, several options could be envisioned to revisit and adapt the ICH S7A i) to support Phase I trials and encapsulating non-clinical assessment of key safety liabilities supporting all clinical phases alongside clinical guidance; or ii) to support Phase I trials, supplemented by independent stand-alone non-clinical and clinical guidance addressing key safety liabilities or iii) to support Phase I trials, supplemented by stand-alone integrated multidisciplinary (M) non-clinical and clinical guidance addressing key safety liabilities. Irrespective of the option chosen, and as captured on Fig. 2, several key features would need to be considered as input, considering the latest available scientific, technological, operational approaches to deliver an optimal output.

CRediT authorship contribution statement

Jean-Pierre Valentin: contributed to, Conceptualization, Visualization, Supervision, Project administration. **Derek Leishman:** contributed to, Conceptualization, Visualization, Supervision, Project administration.

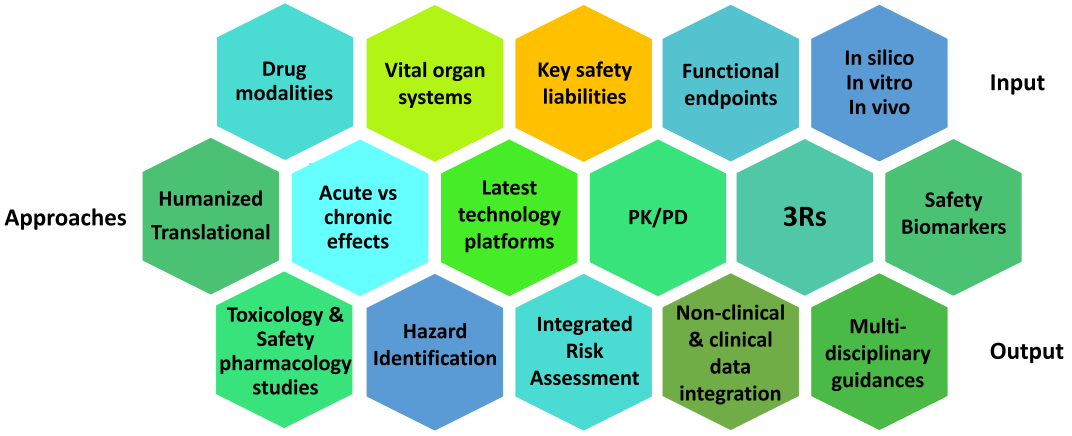

Fig. 2. Non-exhaustive, list of key features to consider for revamping the ICH S7A guideline. Several inputs would have to be considered alongside the latest scientific, technological, and operational approaches to deliver meaningful output.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Jean-Pierre Valentin reports a relationship with UCB Biopharma SRL that includes: employment. Derek Leishman reports a relationship with Ely Lilly that includes: employment. Drs Valentin and Leishman are members of the ICH E14/S7B Implementation Working Group (IWG) representing the EFPIA and PhRMA, respectively. Both are Past-Presidents of the Safety Pharmacology Society (https://safetypharmacology.org/), in 2014 and 2013 respectively.

Data availability

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

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