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Principles of Safety Pharmacology

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Preface

Safety pharmacology has evolved from a mixture of toxicological investigations to what we now recognize as a frontloaded integrated risk assessment during the 20 years that has followed the recognition of rare but potentially lethal adverse drug reactions, exemplified by terfenadine-induced torsades de pointes. Safety pharmacology is most important during the period of preclinical drug discovery and development. Safety pharmacology has evolved into an astute and flexible discipline and now paradoxically leads the way in discovery standardization by virtue of the efforts that have taken place to validate preclinical methods. Numerous examples exist where a collection of positive and negative controls are used to template a method—an approach rarely reciprocated in such detail and with such diligence in Discovery pharmacology.

In this volume, we have assembled reviews of all the main aspects of preclinical and translational safety pharmacology, with emphasis on explanation for choice of approach and the testing of validity. The articles are intended to serve as reference for industry and text for the growing undergraduate and postgraduate programs and courses on safety pharmacology that are emerging in universities worldwide.

Raritan, NJ, USA — Michael K. Pugsley
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Part I

An Overview of Safety Pharmacology and Its Role in Drug Discovery

A Historical View and Vision into the Future of the Field of Safety Pharmacology

Alan S. Bass, Toshiyasu Hombo, Chieko Kasai, Lewis B. Kinter, and Jean-Pierre Valentin

"1. Don't do something just because you can.
2. Don't do something just because it has always been done.
3. Don't do something just because others do it."
"4. Don't do something because (you believe) it is expected.
5. Don't do something the results of which cannot be interpreted.
6. Do something because there is a reasonable expectation it will provide knowledge necessary for an accurate decision."

Gerhard Zbinden and Robert Hamlin (Hamlin 2006)

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Abstract

Professor Gerhard Zbinden recognized in the 1970s that the standards of the day for testing new candidate drugs in preclinical toxicity studies failed to identify acute pharmacodynamic adverse events that had the potential to harm participants in clinical trials. From his vision emerged the field of safety pharmacology, formally defined in the International Conference on Harmonization (ICH) S7A guidelines as "those studies that investigate the potential undesirable pharmacodynamic effects of a substance on physiological functions in relation to exposure in the therapeutic range and above." Initially, evaluations of small-molecule pharmacodynamic safety utilized efficacy models and were an ancillary responsibility of discovery scientists. However, over time, the relationship of these studies to overall safety was reflected by the regulatory agencies who, in directing the practice of safety pharmacology through guidance documents, prompted transition of responsibility to drug safety departments (e.g., toxicology). Events that have further shaped the field over the past 15 years include the ICH S7B guidance, evolution of molecular technologies leading to identification of new therapeutic targets with uncertain toxicities, introduction of data collection using more sophisticated and refined technologies, and utilization of transgenic animal models probing critical scientific questions regarding novel targets of toxicity. The collapse of the worldwide economy in the latter half of the first decade of the twenty-first century, continuing high rates of compound attrition during clinical development and post-approval and sharply increasing costs of drug development have led to significant strategy changes, contraction of the size of pharmaceutical organizations, and refocusing of therapeutic areas of investigation. With these changes has come movement away from dedicated internal safety pharmacology capability to utilization of capabilities within external contract research organizations. This movement has created the

opportunity for the safety pharmacology discipline to come "full circle" and return to the drug discovery arena (target identification through clinical candidate selection) to contribute to the mitigation of the high rate of candidate drug failure through better compound selection decision making. Finally, the changing focus of science and losses in didactic training of scientists in whole animal physiology and pharmacology have revealed a serious gap in the future availability of qualified individuals to apply the principles of safety pharmacology in support of drug discovery and development. This is a significant deficiency that at present is only partially met with academic and professional society programs advancing a minimal level of training. In summary, with the exception that the future availability of suitably trained scientists is a critical need for the field that remains to be effectively addressed, the prospects for the future of safety pharmacology are hopeful and promising, and challenging for those individuals who want to assume this responsibility. What began in the early part of the new millennium as a relatively simple model of testing to assure the safety of Phase I clinical subjects and patients from acute deleterious effects on life-supporting organ systems has grown with experience and time to a science that mobilizes the principles of cellular and molecular biology and attempts to predict acute adverse events and those associated with long-term treatment. These challenges call for scientists with a broad range of in-depth scientific knowledge and an ability to adapt to a dynamic and forever changing industry. Identifying individuals who will serve today and training those who will serve in the future will fall to all of us who are committed to this important field of science.

Keywords

Safety pharmacology • Cardiovascular system • Central nervous system • Peripheral nervous system • Respiratory system • INTERNATIONAL CONFERENCE ON HARMONIZATION • ICH S7A • ICH S7B • ICH E14 • United States Food and Drug Administration • European Medicines Agency • Japan Pharmaceutical and Medicines Devices Agency

List of Abbreviations

ABPI	Association of the British Pharmaceutical Industry
ADRs	Adverse Drug Reactions
AEs	Adverse Events
APD	Action Potential Duration
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte which is the Federal Institute for Drugs and Medical Devices
CFR	Code of Federal Regulations
CiPA	Comprehensive In vitro Proarrhythmia Assay
CNS	Central Nervous System
CPMP	Committee for Proprietary Medicinal Products

CROs	Contract Research Organizations
CSRC	Cardiac Safety Research Consortium
DSP	Diplomate in Safety Pharmacology
ECG	Electrocardiogram
ECVAM	European Centre for the Validation of Alternative Methods
EFPIA	European Federation of the Pharmaceutical Industry Association
eIND	Exploratory Investigational New Drug Application
EMEA	European Medicines Agency
EU	European Union
EWG	Expert Working Group
FDA	United States Food and Drug Administration
GLP	Good Laboratory Practice
hERG	human Ether-a-go-go-Related Gene
ICH	International Conference on Harmonization
ILSI	International Life Sciences Institute
IWG	Implementation Working Group
HESI	Health and Environmental Sciences Institute
IND	Investigational New Drug Application
iPSCs	Induced pluripotent stem cells
JACL	Japan Association of Contract Laboratories for Safety Evaluation
JNDA	Japanese New Drug Applications
JPMA	Japanese Pharmaceutical Manufacturers Association
MHLW	Ministry of Health, Labour and Welfare
MHW	Ministry of Health and Welfare
NCEs	New Chemical Entities
NDAs	New Drug Applications
PhRMA	Pharmaceutical Research and Manufacturers of America
Q&As	Questions and Answers
QT	Duration of the QT interval of the cardiac electrocardiogram
QT PRODACT	QT Interval Prolongation: Project for Database Construction
R&D	Research and Development
SEND	Standard for Exchange of Nonclinical Data
SP	Safety pharmacology
SPS	Safety Pharmacology Society
JSPS	Japanese Safety Pharmacology Society
TDP	Therapeutic Products Directorate
TQT	Clinical Thorough QT study
USA	United States of America

Professor Gerhard Zbinden argued that the major clinical endpoints related to safety in early human trials were not adequately evaluated in the routine animal safety studies being carried out in the 1970s, where the focus was on pathomorphological

and lab parameters appearing late during treatment, while damages of bodily functions appear early. This different focus posed a significant and underappreciated risk to healthy normal volunteers and patients participating in early clinical evaluations of new drugs (Zbinden 1979). Zbinden's hypothetical "gap" was dramatically exposed in the mid-1990s, when it became apparent that individuals were being placed at an unacceptable risk of cardiac toxicity and death from drugs that were marketed for treatment of a variety of non-life-threatening diseases (Shah 2002b). In response, the fledgling field of safety pharmacology was formalized in international regulatory guidance, marking rapid recognition of its contributions to protecting clinical trial subjects (Bass et al. 2004b, 2011). In the intervening years, advances in science and technology and contributions from regulators, scientists, and the public have challenged safety assessment of new drugs, and safety pharmacology in particular, to evolve quickly, sometimes ahead of scientific consensus and governing regulations. Added to this landscape are the growing economic challenges and a business model for the discovery and development of new drugs that many claim is not sustainable as evidenced by the higher difficulties of bringing new drugs to market, despite continuous attempts to alter the model to increase the probability of success (Hay et al. 2014; Holdren et al. 2012; Urban et al. 2014).

Accounting for the relatively brief history of safety pharmacology, the authors have laid out a review of the discipline, from the time of Dr. Zbinden to the present day, as well as forecasting the future from their vantage points of leaders deeply committed and involved in the growth of the field. The periods covered in this chapter include the time prior to adoption by the International Conference on Harmonization (ICH) the topics of guidelines which would ultimately govern the regulatory practice of safety pharmacology, the trials, tribulations, and constantly evolving challenges associated with the implementation of the laboratories conforming with those guidelines and the scientific and intellectual growth and maturation of the field that was aligning and adapting to the changing scientific and regulatory landscape and business environment of the pharmaceutical industry. The chapter concludes with thoughts on the future challenges faced by safety pharmacology and the scientists that will shepherd the continued evolution of this discipline, as those scientists will also be expected to anticipate and respond to the events that will unfold over the coming years.

1 Prior to Adoption of ICH S7: Safety Pharmacology/General Pharmacology

Like any other profession or scientific discipline, safety pharmacology has its beginnings, in terms of name, concepts, discipline, practices, philosophy, and specific tests. Gerhard Zbinden (1979) is generally credited with calling attention to the "disconnect" between the study endpoint (e.g., histopathology) of standard nonclinical toxicological test procedures of that era and the types of adverse drug reactions (ADRs) observed by clinicians in clinical trials: that whereas the former

focused heavily upon morphological and biochemical lesions, the latter were focused on organ functional side effects. Further, in an era when clinical chemistry and histopathology were dominant in nonclinical safety testing, Zbinden raised the specter that potentially life-threatening functional side effects of concern to physicians and patients could be discovered only late in standard toxicological testing. Zbinden's warning was dramatically substantiated in the mid-1990s with the recognition of drug-related "long-QT" syndrome and risk of a potentially fatal ventricular tachyarrhythmia (Anon 2005a, 2014; Bass et al. 2005, 2007, 2008; Borchert et al. 2006; Darpo 2010; Darpo et al. 2006; Kinter et al. 2004; Shah 2002a, b, 2007). Thus, there can be little debate that G. Zbinden is the "father" of what is known today as modern safety pharmacology. Ironically, Zbinden was also an advocate of the value of rat models for cardiovascular assessments of drugs, but we now recognize that this rodent species is an inappropriate model with which to detect drug-induced long-QT effects because the rat relies on a different cardiac delayed-rectifying potassium current (I_{Kr}) for cardiac repolarization than that used by humans (see below).

The first explicit references to safety pharmacology in regulatory guidances for investigations of potential for undesirable pharmacological activities in pharmaceutical research and development (R&D) appeared in ICH documents and subsequent FDA release of the ICH S6 guidance document in July 1997: '*Safety Pharmacology studies measure functional indices of potential toxicity. … The aim of the Safety Pharmacology studies should be to reveal any functional effects on the major physiological systems* (e.g., *cardiovascular, respiratory, renal, and central nervous systems).*' (Anon 2012a, b), and '*Safety Pharmacology includes the assessment of effects on vital functions, such as cardiovascular, central nervous, and respiratory systems, and these should be evaluated prior to human exposure*' (Anon 1997b, c). These "original concepts" of safety pharmacology were subsequently codified in separate ICH guidance documents ICH S7A (Anon 2001c, e) and ICH S7B (Anon 2005a, b) and established safety pharmacology as it applies to the development of new pharmaceutical agents today (Fig. 1).

What is uncertain is the origin of the term "safety pharmacology" within the context of the ICH guidance. In prior regional guidance documents, the concepts framed and subsequently fleshed out in the 1997 and 2000 ICH documents included components embedded in "general pharmacology" studies (Lumley 1994) and in a description of "pharmacological toxicity" testing (Williams 1990). While Kinter et al. (1994) listed the term "safety pharmacology" as one of several then currently in use to identify investigations of "effects of a new drug on pharmacological targets and organ functions, other than those for which the drug was intended," one of those authors (LK) recalls it was included because safety pharmacology was being used in then early drafts of the 1996 ICH documents. Dr. Gerd Bode, a member of the ICH S7A Expert Working Group (EWG, Table 1), recalls that in the early 1990s ICH defined three disciplines for which guidelines should be drafted: quality, safety, and efficacy. Safety in the original ICH sense was preclinical safety, or preclinical toxicology (i.e., nonclinical testing for unexpected adverse events). Dr. Bode recalls that at that time investigations for adverse functional effects as part

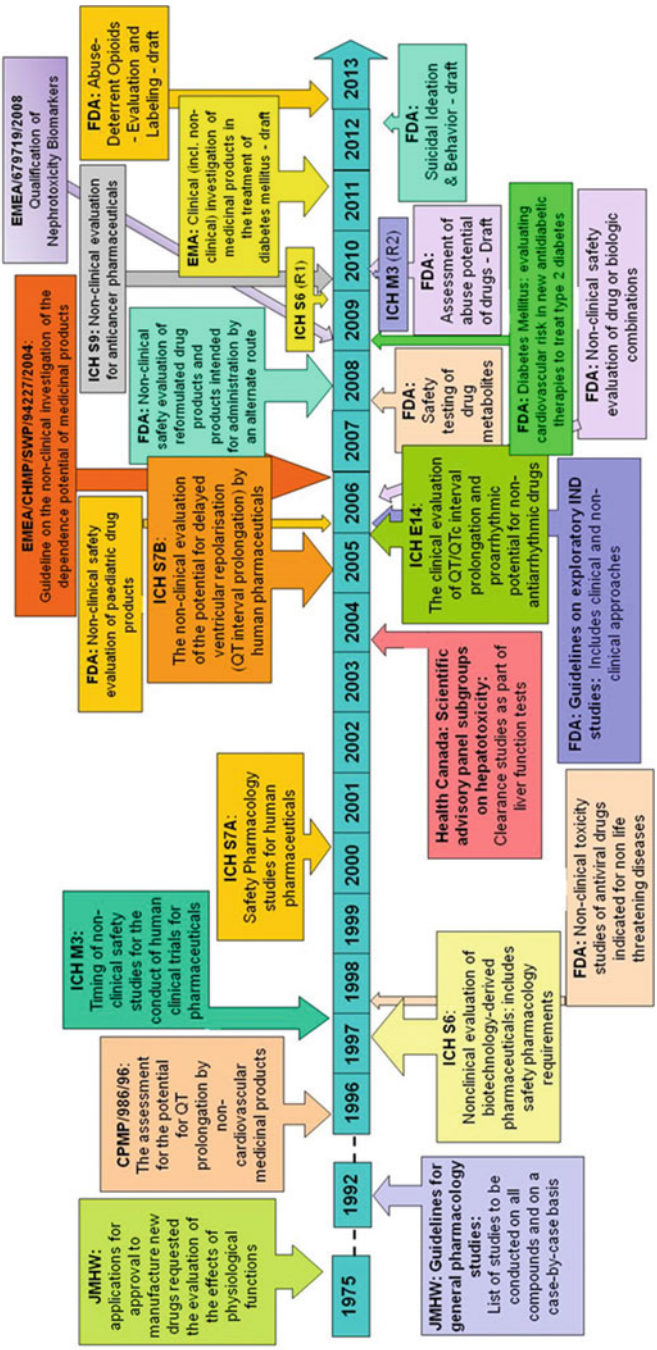

Fig. 1 Scope and implementation date of regulatory guidance documents referring entirely or in part to safety pharmacology over the last 40 years. Over the last decade, there has been an increase in the number and scope of regulatory guidance referring to safety pharmacology endpoints reflecting increasing regulatory concerns. *FDA* United States Food and Drug Administration, *ICH* International Conference on Harmonization, *JMHW* Japanese Ministry of Health and Welfare, *EMEA* European Agency for the Evaluation of Medicinal Products, *CPMP* Committee on Proprietary and Medicinal Products, *CHMP* Committee on Medicinal Products for Human Use

Table 1 ICH-S7A Expert Working Group members

Party	Experts	
MHW	Kannosuke Fujimori (OPSR)[a]	Yoichi Sato (MDEC)
JPMA	Munehiro Hashimoto (Pharmacia and Upjohn)[b] Hiroshi Mayahara (Takeda)	Toshiyasu Hombo (Fujisawa)
EU	Klaus Olejniczak (BfArM)	
EFPIA	Gerd Bode (HMR)	Andrew Sullivan (GW)
FDA	Joseph DeGeorge (CDER)	Martin Green (CBER)
PhRMA	James Moe (Pharmacia and Upjohn) Kenneth Ayers (GW)	Richard Robertson (DuPont)
EFTA	Jurg Seiler (IKS)	
Canada	Peter Grosser (Health Canada)	

[a]Rapporteur from Step 2 through Step 4
[b]Rapporteur from Step 0 though Step 2 sign-off
JMHW Japanese Ministry of Health and Welfare, *JPMA* Japanese Pharmaceutical Manufacturers Association, *EU* European Union, *EFPIA* European Federation of Pharmaceutical Industry Association, *FDA* United States Food and Drug Administration, *PhRMA* Pharmaceutical Research Manufacturers Association, *EFTA* European Free Trade Association, *OPSR* Organization for Pharmaceutical Safety and Research, *MDEC* Medical Device Evaluation Committee, *P&U* Pharmacia and Upjohn, *BfArM* German Federal Institute for Drugs and Medical Devices, *HMR* Hoechst Marion Roussel, *GW* Glaxo Wellcome, *CDER* Center for Drug Evaluation and Research, *CBER* Center for Biologic Evaluation and Research, *IKS* Swiss Kontrollstelle fur Heilmittel

of then "general pharmacology" investigations were redefined incorporating the ICH safety definition; hence "safety pharmacology" appeared first in draft versions of the ICH S6 guideline in 1995. Thus, the term "safety pharmacology" appears to arise de novo in the early 1990s as an amalgamation of the then current general pharmacology terminology and new ICH definition for safety guidance in pharmaceutical development.

Also unclear is why the new term "safety pharmacology" was deemed necessary when "general pharmacology" was both inclusive and common in both regulatory and industry parlance. The regional regulatory guidance that predated the 1997 ICH guidance defined general pharmacological studies as those that revealed both potential useful and harmful properties of a drug in a quantitative manner which permits an assessment of therapeutic risk (Australian NDF4 guidelines, see Lumley, 1994). Williams (1990) referred to general pharmacological properties and pharmacological profiling of candidate drugs that result in unintended or undesirable effects as "pharmacological toxicity." The general guidance included in the Japanese Guidelnes for Toxicity Studies for Drugs (Anon 2001b; an English version of the guidance published by Anon 1995) recommended specific general pharmacology studies to be conducted on all investigational drugs (List A) and additional studies to be conducted "when necessary" (List B). In a paper entitled "The Role of Pharmacological Profiling in Safety Assessment," reviewing the Japanese Lists A and B, Kinter et al. (1994), the authors identified two separate categories of tests: "A. . .test in which the drug is administered to an intact or acutely-prepared animal model for the purpose of assessing the adverse events

. . .(safety profiling)" and a ". . . test in which a drug is evaluated for (1) affinity for a pharmacological target, (2) activity to stimulate, inhibit, . . .(3) activity to stimulate, potentiate,. . . activity of another drug, or (4) activity to stimulate, potentiate, . . . physiological or pharmacological responses. . . (pharmacological profiling)." They further observed that safety profiling (which they labeled "safety pharmacology") was limited to those organ systems of critical interest to primary care physicians (cardiovascular, respiratory, central nervous system (CNS), renal and gastrointestinal) and contributed directly to drug discovery, risk assessment, and patient management, whereas pharmacological profiling (labeled "general pharmacology") cataloged mechanisms by which drugs might impact an organism and were limited only by imagination and available resource. These concepts were further refined in ICH S7A (Anon 2001c, e) to specify drug effects upon the intended pharmacological target (primary pharmacology), drug effects on targets other than the primary target (secondary pharmacology), and drugs effects that adversely impact critical organ functions (safety pharmacology), the definitions in general use today. Thus, the "new" term, safety pharmacology, was needed to delineate the concepts of pharmacologically based toxicity (or safety profiling) from pharmacological profiling, congruent with Dr. Bode's recollection of the term itself (see above).

Functions conducting general pharmacology and/or safety pharmacology studies were distributed across research (discovery) and development (e.g., toxicology) organizations in different companies and viewed the primary value of those investigations as supporting additional/alternative therapeutic applications and/or detection of potential safety hazards (see Williams 1990). This dichotomy of purpose was reflected in the name of an informal pharmaceutical industry trade group of that era—the General Pharmacology/Safety Pharmacology Discussion Group [the progenitor of the current Safety Pharmacology Society (Bass et al. 2004b)]. However, by the time of adoption of the ICH S7A and ICH S7B guidelines (described later in this chapter), the functional responsibilities for safety pharmacology became better defined. In surveys of industry practices carried out by the newly incorporated Safety Pharmacology Society in 2005 and again in 2008, the majority of work across the industry was found in toxicology departments responsible for regulatory studies complying with Good Laboratory Practice (GLP) (Friedrichs et al. 2005; Lindgren et al. 2008; Valentin et al. 2005).

Kinter and Dixon (1995) described a safety pharmacology program for pharmaceuticals wherein they advocated for a tiered approach to testing drug effects on major organ functions:

- Core: cardiovascular, neurological and neuromuscular, respiratory, and renal that are of greatest interest to clinicians
- Special: ocular and auditory functions that address specific pharmacological or chemical class issues
- Ancillary: gastrointestinal, autonomic, and behavioral and drug interactions that satisfy then divergent regional regulatory requirements

Williams (1990) posited that acute or single-dose studies were generally sufficient and that doses selected for pharmacological profiling should "span the

pharmacological and toxicological range in order to provide data on effects occurring at therapeutic as well as potentially toxic levels of exposure." The Kinter and Dixon (1995) paper expanded those concepts to include conduct of safety pharmacology studies to support Phase I clinical trials in humans. This was a fundamental shift from the then current Japanese guidelines that required such studies only prior to registration (Anon 1995). The use of unanesthetized animals and clinical route of administration in order to model the dose route in the single ascending dose phase in healthy normal volunteers, assessment of test article exposure in safety pharmacology studies, and conduct of core safety pharmacology studies in compliance with GLP (Anon 2004b, 2000b) regulations were also advocated by Kinter and Dixon (1995), although the latter was first presented in a European regulatory guidance note (Anon 2004b). Also presented was a new objective: "to identify organ function markers of efficacy and toxicity for support of early clinical studies in humans" (e.g., safety pharmacology biomarkers). In a subsequent paper, the use of cardiovascular telemetry for safety pharmacology evaluations in conscious animals was first described (Kinter et al. 1997). It is noteworthy that the journal *Drug Development Research*, Volume 32 (1994), contains several papers delineating then current practices in cardiovascular, CNS, respiratory, and renal safety pharmacology and results of the first comprehensive industry safety pharmacology survey. All of these concepts were subsequently included at least in part in ICH S7A (Anon 2001c, e).

A final "origin" is that of the specific testing paradigms included in the Japanese general pharmacology guidelines Lists A and B (Anon 1995) and by Williams (1990) as these predate the concepts of pharmacological toxicity, safety profiling, and safety pharmacology (see above). Williams (1990) states that "Typically a battery of 30–40 specialized pharmacological tests is conducted to support drug registration in Japan. Such testing is performed on all classes of pharmaceutical agents, regardless of therapeutic class." One of the current authors (LK) concurs with this statement based upon his review of regulatory study packages presented for registration in Japan during the late 1980s. Those "specialized pharmacological tests" were the in vivo and in vitro bioassays used by pharmacologists to identify potentially useful pharmacological activities before they were replaced by in vitro studies of efficacy (on-target) and off-target sites employing molecular interaction (e.g., ligand–receptor binding assays) screens in the late 1970s. The transition of laboratory practices to the principles of safety pharmacology was intended to focus work of safety scientists on a core of organ functions that were viewed as important to human safety and away from the broad general requirements of the Japanese general pharmacology guidelines, which at the time was of concern to the pharmaceutical industry.

Implementation of safety pharmacology programs compliant with current guidances came about as the transition of carrying out "ad hoc" general pharmacology bioassays of small molecules and biologics following tailored protocols as an ancillary activity of discovery laboratories, to a concerted responsibility of safety pharmacology programs to identify those pharmacodynamic properties with the potential to place clinical trial subjects and patients at risk (Bass et al. 2004a). This focused pharmacodynamic testing began in the early to late 1990s with the appearance of a minimal number of safety pharmacology programs in the United States of

America (USA) and Europe Union (EU) and expanded to, in the first several years following adoption of ICH S7A (2001), a greater number of institutions with established Departments of Safety Pharmacology (Lindgren et al. 2008). Programs in safety pharmacology in Japan were well established and preceded the adoption of the ICH guidelines as a result of the Japanese requirements for general pharmacology. The transition from an "ad hoc approach" to a systematic series of pharmacodynamic assays of the major organ system functions, originally framed in the draft guidances of EU, Japan, and USA (Bass et al. 2004a), led to a Step 0 ICH document on safety pharmacology, which ushered in the beginning of deliberations to define the guidances, ICH S7A and ICH S7B.

2 Eight Years of Deliberations Leading to Step 4 of Two Guidances: Insights into the Expert Working Groups (EWG) Responsible for ICH S7A and ICH S7B Guidances

The mission of the ICH is ". . . to make recommendations towards achieving greater harmonisation in the interpretation and application of technical guidelines and requirements for pharmaceutical product registration, thereby reducing or obviating duplication of testing carried out during the research and development of new human medicines. . .." ICH was established in 1990 and the reader is directed to its website (http://www.ich.org) and the recent publication (van der Laan and DeGeorge 2013) to learn more about the workflow followed by the respective EWGs, who were given the responsibility of crafting two separate guidance documents governing the practice of safety pharmacology.

The development of the international regulatory guidelines concerning safety pharmacology encompassed the period from the evolution of the Step 0 document in 1997 to the final Step 4 document, ICH S7A in 2000, and the emergence of a new topic specific to detecting proarrhythmic risk associated with QT prolongation, with a Step 0 document, ICH S7B in 2000 to the final Step 4 document in 2005. Regional adoption of each of the guidances occurred in the same or following year in the USA and EU, but the adoption of the guidelines in Japan took longer, especially in the case of ICH S7B. In Japan, the ICH S7A guidance went into effect in 2001, but was not fully implemented until 2003 to allow institutions time to establish the necessary GLP compliant capabilities (Valentin et al. 2005). Although the laboratories in Japan had extensive experience with the technical aspects of carrying out the core studies required by the ICH S7A Safety Pharmacology guideline as a result of having worked under the requirements for Japanese General Pharmacology guidance (Anon 1995), the requirement for conformance with GLPs required additional time. With the adoption of ICH S7A in Japan, the Japanese general pharmacology guideline was formally retired. The implementation of the ICH S7B guidance was delayed until 2009 to accommodate the timeframe needed for the implementation of the clinical guidance on assessing QT interval prolongation, ICH E14 in Japan. The events and timing leading up to the respective Step 4 documents are chronicled below.

2.1 S7A Safety Pharmacology Studies for Human Pharmaceuticals (1998–2000)

The topic to develop harmonized guidelines on the practice of safety pharmacology was proposed to the ICH—Steering Committee by the Japanese delegates (Japanese Pharmaceutical Manufacturers Association (JPMA) and Ministry of Health and Welfare [MHW; now referred to as the Ministry of Health, Labour and Welfare (MHLW)], in 1997, and adopted as the Topic S7 in 1998. The membership of the ICH S7 EWG and a chronicle of the timelines and milestones are presented in Tables 1 and 2, respectively.

The first meeting was held in Brussels in March 1999, where the EWG assembled to consider the Step 0 document. The Step 0 document was a compilation of the major principles held in the draft working documents of the participating nations (Bass et al. 2004a). Thereafter, the draft document advanced to a sign-off of the Step 2 version in the fourth EWG meeting in Tokyo in March 2000. In accordance with the ICH process, achieving Step 2 signaled the transition of the role of rapporteur from the pharmaceutical industry member to the regulatory member of the EWG. Since the original recommendation for the ICH topic was made by the JPMA and MHW, the responsibility of rapporteur fell to Dr. Kannosuke Fujimori, the MHW member. Also in accordance with the process laid out by the ICH, an additional milestone of achieving Step 2 was that this was the only time that the pharmaceutical industry members of the EWG have signatory responsibility for the draft ICH document. On the other hand, responsibility for content, scientific background, and strategies continued throughout the whole drafting process for both parties (regulators and industry), and this common responsibility was (independent of signatures) assured via the ICH Steering Committee. At Step 4, only the regulatory members of the ICH EWG serve as signatories to the final ICH document. Step 4 of ICH S7 was achieved in the sixth EWG meeting in San Diego in November 2000. For a more detailed description of the recommendations of ICH 7 (which became ICH S7A at the time of Step 4 adoption; this was to accommodate diverging interpretations within the EWG

Table 2 Chronology of ICH S7A Expert Working Group (EWG) meetings

EWG meeting	Date	Place	Step
First	March 1999	Brussels	1
Second (extra)	August 1999	Tokyo	1
Third	October 1999	Washington, DC	1
Fourth	March 2000	Tokyo	2
Fifth (extra)	September 2000	Bern	3
Sixth (ICH-5)	November 2000	San Diego	4

Note: Extra refers to two meetings held by the ICH S7A EWG that were outside of the regularly scheduled meetings of the ICH Steering Committee; ICH-5 was the fifth conference of ICH that had taken place since ICH was established in 1990; the reader is referred to the ICH website for a definition of the ICH Process (http://www.ich.org)

to recommend guidelines on the study of cardiac ventricular repolarization, which as a result became a new topic designated ICH S7B), the reader is referred to the chapter "Safety Pharmacology: A Practical Guide" (Bass and Williams 2003).

That the ICH S7A document could reach Step 4 in the short time period of only 1 year and 8 months was unprecedented and attributed, in part, to the quality of the Step 0 document that reflected the collective positions of each of the tripartite regulatory members: Guideline for Safety Pharmacology Study by the Japanese MHW, Concept paper on nonclinical safety pharmacology studies by the USA Food and Drug Administration (FDA), and Note for Safety Pharmacology Studies in Medical Products Development by the European CPMP, see Bass et al. (2004a).

2.2 Hierarchy of Organ Systems, Categorization of Safety Pharmacology Studies, and GLP Compliance

As described earlier, the "General Pharmacology Study Guideline" established by MHW in 1991 was the only guideline recognized across the pharmaceutical industry that came close to the present day guidance for safety pharmacology (Anon 1991, 1995). This guideline did not require formal and full compliance with GLP, but did require data collection conforming with the Japanese system of "raw data check," which was a level of documentation that allowed reconstruction of a study by the regulator. The Japanese guidelines clearly specified more than 10 types of bioassays encompassing the evaluation of seven different systems, including general activity and behavior, CNS, autonomic nervous system and smooth muscle, respiratory and cardiovascular systems, digestive system, water and electrolyte metabolism, and other organ systems in which activity would be expected based on class- or chemotype-related pharmacodynamic effects from studies of related drugs (Anon 1991, 1995). These studies were referred to as category A studies and were expected for advancing all new test agents into early clinical trials in Japan (Anon 1995), although the study data itself were not reviewed by the Japanese regulators until the time of the JNDA.

In the first meeting in Brussels in 1999, it was unanimously agreed that safety pharmacology studies should be conducted in compliance with GLP, as was the standard for other nonclinical ICH safety guidances (Anon 2004b, 2000b). Most of the discussions in the subsequent EWG meetings were spent deliberating over the necessity of studying specific organ systems, study objectives, and the designs and parameters used in the evaluation of new molecular entities, primarily small molecules.

The concept of "Hierarchy of Organ Systems" was introduced where three organ systems, i.e., the cardiovascular, respiratory, and central nervous systems of which functions are acutely critical for life, were considered to be the most important to assess as the safety pharmacology battery. The study of each of these organ systems was to be conducted with all test agents, irrespective of their targeted indication or chemical class and they were referred to as the "Safety Pharmacology Core Battery." It was also agreed that such studies should ordinarily be conducted in compliance

with principles of GLP and only general study designs were described. The EWG wished to limit the scope of the core battery exclusively to the three critical organ systems for the reason described above, but as safety pharmacology was originally envisioned in the early draft of the ICH S6 guideline (Anon 2012a, b), the study of the renal system had also been described. The request to study renal function before FIM continues to be part of ICH S6 despite its revision in 2009, but in practice, this functional test is not asked for at that early time of development by regulators, except if there is concern.

At the meeting in Brussels, consensus of the members was also achieved that "follow-up studies" of the "core battery" would be conducted to provide a greater depth of understanding of the pharmacodynamic properties of the molecular entity than that provided by the standard designs of the core battery studies. There was also agreement that the follow-up studies would be uniquely designed to test specific hypotheses. Although not comprehensive, a list of examples of different types of follow-up studies were cited in the guidelines. The EWG also devised another category of studies, the "supplemental" study, which were carried out when evaluation of other organ systems (e.g., renal/urinary system, autonomic nervous system, gastrointestinal system, etc.) was required. The EWG agreed that the "follow-up" and "supplemental" studies should be conducted in compliance with GLP to the greatest extent feasible and that at minimum having sufficient documentation to assure being able to reconstruct the study would be of greatest importance.

In addition to the categorizations described above, two other categories of pharmacodynamic studies were described in the ICH S7A guidelines at the request of ICH M4S EWG (Anon 2001a, d). These included the primary pharmacodynamic and secondary pharmacodynamic studies, which were described in order to distinguish the requirement for GLP compliance for safety pharmacology studies, but not for primary or secondary pharmacodynamic studies.

2.3 General Considerations on In Vivo Studies

In conducting in vivo studies, it is preferable to use unrestrained, unanesthetized animals that are conditioned to the laboratory environment, always paying attention to the welfare of animals. In the discussions of the use of unanesthetized animals, the avoidance of discomfort or pain was considered of foremost importance. The EWG said that in well-characterized in vivo test systems, the repeated study of positive control agents may not be necessary. The latter is indicative of the animal welfare practice of the 3Rs (reduction, refinement, and replacement (Holmes et al. 2010). With regard to biotechnology-derived products that achieved high specific receptor targeting that has been demonstrated in an appropriate animal species, the EWG made a definitive statement that it is often sufficient to evaluate safety pharmacology endpoints as a part of toxicology and/or pharmacodynamic studies (provided that exposure data are available in the latter). As a result, with such strategy separate safety pharmacology core battery studies need not be

conducted. This principle is considered to be one of the reasons for a recent trend toward combining safety pharmacology endpoints into toxicology studies (Redfern et al. 2013; Vargas et al. 2013). Altogether safety pharmacology should not be considered as a stand-alone discipline. Close cooperation among safety pharmacology, pharmacokinetics, and toxicology can facilitate the overall development of a new molecule. Like all safety studies, safety pharmacology needs to be supported with drug pharmacokinetic information, but that could, for example, be derived from toxicology studies. The combined knowledge from these disciplines can optimize the calculation of safety margins (as outlined by Redfern et al. 2003). Another example is the selection of the high dose in safety pharmacology studies; here toxicity data can help to justify the limit of the top dose selected.

However, upon reflection by the safety pharmacology community over the past almost 15 years, the view that safety pharmacology endpoints can be incorporated into toxicology studies has been challenged, particularly in the case of cardiovascular measurements. Scientists have recognized that the level of precision of cardiovascular safety pharmacology endpoints collected in dedicated safety pharmacology studies could not be reproduced without careful attention to the study conditions in definitive toxicology studies (Guth et al. 2009; Leishman et al. 2012; Pettit et al. 2009; Redfern et al. 2013). This awareness has led vendors to develop technologies that can be adapted to toxicology studies in order to mitigate the imprecision of many of the standard methods that existed at that time. Included are systems to evaluate cardiovascular and respiratory function, e.g., electrocardiogram (ECG), blood pressure, and respiratory rate and volume using jacketed technologies; see reviews from Authier et al. (2013) and Redfern et al. (2013). In addition, a similar concern has prompted organizations to introduce dedicated trained staff capable of studying CNS function in the course of subchronic and chronic toxicity studies. Together, this heightened sensitivity to the quality of data used in the decision making and emergence of technical and scientific capabilities has enhanced the confidence in the critical data from toxicology studies that are used to assess the pharmacodynamic risk posed by intermediate- to long-term exposure to small molecules and biologics.

Cardiovascular telemetry, which was strongly recommended by the FDA for in vivo studies, was a relatively new technology at that time of the ICH S7 deliberations. The introduction of the telemetry systems facilitated the conduct of in vivo studies in unrestrained, unanesthetized animals acclimated to the experimental conditions, enabling evaluation of the standard cardiovascular core battery endpoints (e.g., blood pressure, heart rate, and ECG) and allowing the reutilization of animals in subsequent studies. Recognizing the significant advantages offered by this technology, it was strongly embraced by the EWG members as a revolutionary advancement in the conduct of cardiovascular safety studies. Here was a prima facie example of regulation embracement of a new technology that preceded widespread acceptance and incorporation within divisions/laboratories conducting these studies. One author (LK) recalls receiving several communications from international scientists conducting cardiovascular safety pharmacology studies at this time to inquire whether telemetry technology would be acceptable in support of regulatory dossiers.