

Historical review

Origins, practices and future of safety pharmacology

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Abstract

The origins of safety pharmacology are grounded upon observations that organ functions (like organ structures) can be toxicological targets in humans exposed to novel therapeutic agents, and that drug effects on organ functions (unlike organ structures) are not readily detected by standard toxicological testing. Safety pharmacology is "...those studies that investigate the potential undesirable pharmacodynamic effects of a substance on physiological functions in relationship to exposure in the therapeutic range and above..." [International Conference on Harmonization (ICH) S7A guidelines; *Safety Pharmacology Studies for Human Pharmaceuticals*]. This publication provides a comprehensive review of the history of safety pharmacology, international regulatory guidelines that govern the practices of this important field, and the scientific challenges that are being faced by its rapid emergence in pharmaceutical development. The criticality of identifying undesired adverse effects of new drugs in nonclinical models, which reflect the overall human condition, is reflected in the importance of generating an integrated and accurate assessment of possible human risk. The conundrum posed by the challenge of formulating a reliable risk assessment is the importance of improving and enhancing the safe progression of new drugs to the marketplace, while preventing unnecessary delays (or discontinuances), based on nonclinical findings that are not relevant or interpretable in terms of clinical response or human risk.

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"The adverse drug reactions which the standard toxicological test procedures do not aspire to recognize include most of the functional side-effects. Clinical experience indicates, however, that these are much more frequent than the toxic reactions due to morphological and biochemical lesions..." (Gerhard Zbinden, 1979).

1. Origins of safety pharmacology

Serious injury and/or death of volunteers and patients participating in early clinical trials are rare and thus very disturbing when it occurs (Marshall, 2001a, 2001b; Miller,

2000). The organ systems and functions most frequently responsible in these events are the cardiovascular (hypotension, hypertension, and arrhythmia), respiratory (asthma/bronchoconstriction), central nervous (seizure), and renal (glomerular filtration) systems, and the result is almost always a critical care emergency (Kinter, Murphy, Mann, Leonard, & Morgan, 1997). The origins of safety pharmacology are grounded upon observations that organ functions (like organ structures) can be toxicological targets in humans exposed to novel therapeutic agents and that drug effects on organ functions (unlike organ structures) are not readily detected by standard toxicological testing (see Mortin, Horvath, & Wyland, 1997; Williams, 1990; Zbinden, 1984).

Prior to the advent of safety pharmacology, organ function testing was often conducted as an ancillary function of discovery research (Kinter, Gossett, & Kerns, 1994). The selection of specific studies for a candidate drug was based on concerns raised from its primary (those pharmacodynamic effects related to a drug's targeted indication) or

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Table 1
Current international guidelines and draft documents on Safety Pharmacology

| Document | Date | Comment |
|---|------|--|
| <i>Notes on Applications for Approval to Manufacture (Import) New Drugs</i> , issued in 1975 (MHW-Japan) | 1975 | Requested evaluation of ‘...and effects of the test substance on the...central nervous system, peripheral nervous system, sensory organs, respiratory and cardio-vascular systems, smooth muscles including uterus, peripheral organs,...renal function,...and adverse effects observed in clinical studies’ (p.71). |
| <i>Japanese Guidelines for Non-clinical Studies of Drugs Manual 1995</i> . Yakuji Nippo, Tokyo, 1995. | 1995 | Studies in Lists A and B became de facto international blueprints for general/safety pharmacology evaluations until issue of ICH S7A. ‘Normally, anesthetized animals are used,’ hence, anesthetized animal preparation (and particularly the barbiturate-anesthetized dog) became the standard for cardiovascular–respiratory evaluations (p.128). |
| Guideline for Safety Pharmacology Study (draft 3.17, 1998; Japan; personal communication, Dr. K. Fujimori). Committee for Proprietary Medicinal Products (EU). Note for Guidance on Safety Pharmacology Studies in Medicinal Product Development (Draft, 1998) <i>FDA DRAFT Concept paper on safety pharmacology</i> Committee for Proprietary Medicinal Products (EU). Points to Consider: The assessment of the potential for QT interval prolongation by non-cardiovascular medicinal products http://www.emea.eu.int/pdfs/human/swp/098696en.pdf | 1998 | The three regional draft guidelines formed the basis for ICH S7, Draft 0, Safety Pharmacology Studies for Human Pharmaceuticals. As noted below, ICH S7 was adopted in November, 2000, and implemented worldwide in 2001 as ICH S7A, Safety Pharmacology Studies for Human Pharmaceuticals. |
| ICH S6: Preclinical Safety Evaluation of Biotechnology-derived Pharmaceuticals, July 1997 | 1997 | First regulatory document addressing the torsades de pointes (TdP) hazard with pharmaceuticals. Credited with generating academic and interindustrial cooperation to share existing data and to generate collaborative efforts to rapidly produce realistic experimental and clinical approaches for the identification of preclinical signals of a TdP hazard. ‘...The aim of the safety pharmacology studies should be to reveal functional effects on major physiological systems (e.g., cardiovascular, respiratory, renal, and central nervous system). ...’ |
| ICH M3: Non-clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals, July 1997 | 1997 | ‘‘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.’’ |
| Guidance for Industry. S7A Safety Pharmacology Studies for Human Pharmaceuticals. US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, ICH, July, 2001. http://www.ifpma.org/ich5s.html | 2001 | Provides the general study design framework for in vitro and in vivo safety pharmacology evaluations. ‘‘Data from unrestrained animals that are chronically instrumented for telemetry,...’’ Specifically, places evaluations addressing risks for repolarization-associated ventricular tachy-arrhythmia within the safety pharmacology domain (ICH S7B). |
| Therapeutic Products Directorate Guidance Document (Canada). Assessment of the QT prolongation potential of nonantiarrhythmic drugs (2001). http://www.hc-sc.gc.ca/hpb-dgps/therapeut/htmleng/guidmain.html | 2001 | States explicitly that the development of a nonantiarrhythmic drug with a preclinical signal (in vitro or in vivo) of TdP hazard ‘‘should pursued only if it is expected to provide a major benefit for a serious disease or disorder for which safer alternatives are not available, or if the cardiotoxicity is attributable to a metabolite generated in animals, but not in humans.’’ |
| ICH Guideline on Safety Pharmacology Studies for Assessing the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals (S7B), Sept. 2, 2003. | 2003 | Presents a tiered testing scheme recommending in vitro ion current and an in vivo QT assessment in an appropriate species. Provides a current assessment of the pros and cons of available techniques while recognizing that this area is in great flux and recommending that new technologies be evaluated and applied as they become available. |
| The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for nonantiarrhythmic drugs. FDA DRAFT preliminary concept paper. 15 Nov 2002. | 2002 | Accepts ICH S7B guidelines, when finalized, for the preclinical assessment of potential TdP hazard. Provides a starting point for discussion as to how to address preclinical signals within subsequent clinical development. |

Table 1 (continued)

| Document | Date | Comment |
|--|------|--|
| The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for nonantiarrhythmic drugs. ICH E14 Step 1 Draft 2 (July 17, 2003). | 2003 | Uncouples ICH S7B guideline from the clinical evaluation of potential for ventricular repolarization hazard. “Data from these clinical investigations, combined with the results of the data from non-clinical studies, other analyses of ECG waveforms and the clinical cardiac adverse event data are used to make an integrated assessment of proarrhythmic risk for novel drug therapies.” |
| FDA (draft) Guidance for Industry: Non-clinical Studies for development of Pharmaceutical Excipients, February, 2003 | 2003 | “It is recommended that all potential new excipients be appropriately evaluated for pharmacological activity using a battery of standard tests” (see ICH S7 guidance). “It is useful for these data to be obtained at an early point during the development of an excipient, since, if the excipient is found to be pharmacologically active, this information may influence subsequent development.” |
| FDA (draft) Guidance for Industry: Non-clinical Studies for development of Medical Imaging Agents, February, 2003 | 2003 | Table 1: Safety Pharmacology, “Before Phase I: Major organs, and human organ systems the drug is intended to visualize”. |
| CPMP Position Paper on Non-clinical Safety Studies to Support Clinical Trials with a Single Microdose, July, 2003 | 2003 | \$1 Extended single-dose toxicity study and other effects on vital organ function: “. . .In addition, all available background information. . .with respect to vital organ function and other safety parameters obtained in drug screening should be provided.” |
| FDA (draft) Guidance for Industry: Non-clinical Safety Evaluation of Pediatric Drug Products. February 2003 | 2003 | Targets juvenile adult differences in organ system maturation: nervous, reproductive, skeletal, pulmonary, immune, renal, and hepatic (metabolism), (Cardiovascular?) (eight organ systems identified in the ICH S7A safety pharmacology guideline). |

secondary (those pharmacodynamic effects *unrelated* to a drug’s targeted indication) pharmacology, or known effects associated with the drug’s pharmacological, therapeutic, or chemical class. This ad hoc approach to safety evaluation led to nonsystematic decisions regarding study designs and organ systems studied. Often, the study designs employed were those available for the assessment of efficacy, not safety endpoints (e.g., blood pressure determinations in anesthetized felines). In addition, study designs employed dose levels that exceeded the projected clinical efficacy levels by small multiples, if any. Systemic exposures associated with those dose levels were seldom documented; indeed, investigators were sufficiently aware of this criticism that early organ function testing was routinely conducted using intravenous administration, regardless of the intended clinical route of administration (Kinter et al., 1997). These early organ function assessments were often disjointed and disconnected from the results of the toxicology program. Attempts to add organ function endpoints to toxicology protocols were frustrated by the fact that data were collected without regard to the physiological status of the subjects and/or pharmacokinetic parameters (Lufy & Bode, 2002; Morgan et al., 1994).

Prior to 1990, regulatory guidances on organ function testing were limited. The U.S. and European regulations provided only general references to evaluations of drug effects on organ system functions (Gad, 2004; Kinter et al., 1994; Lumley, 1994). Organ function assessments included with investigational new drug applications (INDs) and registrations (NDAs) were inconsistent and often viewed as unimportant (Green, 1995; Proakis, 1994). However, in Japan, the Ministry of Health and Welfare (now

referred to as the Ministry of Health, Labour, and Welfare) had promulgated comprehensive guidances for organ function testing as early as 1975 (see Table 1). These guidelines described which organ systems would be evaluated (including cardiovascular, respiratory, central, and peripheral nervous systems, gastrointestinal, and renal) as a first tier evaluation (Category A studies) and made specific recommendations regarding study designs (including description of models, criteria for dose selection, and which endpoints would be included in the investigation). The guidelines also described a second tier of studies (Category B) to be conducted based on the significant findings in the Category A investigations. Because the Japanese guidelines were the most comprehensive of their time, they became the de facto foundation for organ function safety testing throughout the pharmaceutical industry (Kinter & Valentin, 2002). The organ function studies included in Categories A and B were intertwined with studies whose aim was to catalog additional pharmacological functions and activities (secondary pharmacology) in addition to the primary pharmacological function/activity. Kinter et al. (1994) first distinguished two subgroups of objectives embedded in the Japanese studies as safety and pharmacological profiling. This concept was enlarged upon by the International Conference on Harmonization (ICH) safety pharmacology expert working group to define three categories of pharmacological characterizations: primary and secondary pharmacodynamic, and safety pharmacology (see ICH S7A, Table 1; Bass & Williams, 2003).

During the same period, European, U.S., and Japanese regulatory agencies prepared positions on general pharmacology/safety pharmacology in the form of guidance and

concept papers (Bass & Williams, 2003; Kurata et al., 1997; Table 1). Draft documents appeared from Japan, Europe, and United States by 1998 and were debated at the General Pharmacology/Safety Pharmacology Discussion Group (incorporated as the Safety Pharmacology Society in 2000; <http://www.safetypharmacology.org>) meeting in September of that year. Later that year, the Ministry of Health and Welfare and the Japanese Pharmaceutical Manufacturer's Association proposed to the ICH Steering Committee the adoption of an initiative on safety pharmacology. This proposal was accepted and given the designation of Topic S7.

The origin of the term safety pharmacology is obscure. It first appeared in drafts of the ICH guidelines “Non-Clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals”, Topic M3, and “Preclinical Safety Evaluation of Biotechnology-derived Pharmaceuticals”, Topic S6 (see Table 1). ICH S6 stated that “. . . The aim of the safety pharmacology studies should be to reveal functional effects on major physiological systems (e.g., cardiovascular, respiratory, renal, and central nervous system). . .”. The ICH Topic S7 Expert Working Group began their work in the first quarter of 1999, and a harmonized safety pharmacology guideline was finalized and adopted by the regional regulatory authorities over 2000–2001 (ICH S7A). The guidelines describe the objectives and principles of safety pharmacology, differentiates tiers of investigations (“safety pharmacology core battery,” “follow up,” and “supplemental” studies), establishes the timing of these investigations in relationship to the clinical development program, and embraces GLP procedures (when applicable).

A significant issue that was extensively debated by the ICH Topic S7 Expert Working Group was how to evaluate the potential of new drugs to produce a rare but potentially life threatening ventricular tachy-arrhythmia (torsade de pointes) in susceptible individuals (Ackerman, 1998; Anderson, Al-Khatib, Roden, & Califf, 2002; De Ponti, Poluzzi, & Montanaro, 2001; Haverkamp et al., 2000). The incidence of torsade de pointes with drugs that are targeted at noncardiac indications can be very low, for example, 1 in 120,000, and, hence, the imperative to find nonclinical surrogates to identify those drugs with the potential to elicit this serious cardiac arrhythmia (Malik & Camm, 2001; Moss, 1999; Thomas, 1994; Viskin, 1999; Webster, Leischman, & Walker, 2002). The surrogates of cardiac ventricular repolarization prolongation have included in vitro assessment of drug effects on repolarizing cardiac ion currents (e.g., sodium current, I_{Na} , calcium current, I_{Ca} , rapid, delayed potassium rectifying current, I_{Kr} , slow, delayed potassium rectifying current, I_{Ks} , and inward rectifying potassium current, I_{K1}) and cardiac cell action potential waveforms (Hammond et al., 2001; Redfern et al., 2003), and in vivo electrocardiography assessments of QT interval prolongation (with heart rate correction, QTc), monophasic action potentials, and effective refractory periods (Batey &

Doe, 2003; Hammond et al., 2001; Spence, Soper, Hoe, & Coleman, 1998). The controversial issue is the accuracy of these models to identify problematic drugs and how these data may be assimilated into an assessment of human risk (Kinter & Valentin, 2002). Recognizing that resolution would not be easily forthcoming, the ICH S7 Expert Working Group proposed to the ICH Steering Committee that a new initiative be accepted to generate guidelines on the assessment of drugs for effects on cardiac ventricular repolarization. This proposal was accepted in November 2000 and was designated ICH Topic S7B, “Guideline on Safety Pharmacology Studies for Assessing the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals.” The guidelines on safety pharmacology finalized at the same ICH meeting was redesignated Topic S7A, “Safety Pharmacology Studies for Human Pharmaceuticals.”

A little over a year after the adoption of the ICH Topic S7B, the U.S. Food and Drug Administration and the Pharmaceutical Research and Manufacturers of America proposed to the ICH Steering Committee the adoption of a parallel initiative to prepare guidelines on clinical testing of new therapeutics for their potential to prolong ventricular repolarization. This proposal was accepted as ICH Topic E14, entitled “The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs.” In November 2003, the ICH Steering Committee directed the ICH Topic E14 and S7B expert working groups to align their respective guidelines, in particular, the role that nonclinical findings will serve in the design of the clinical study to assess a drug's effect on ventricular repolarization (QT interval). How these groups ultimately resolve this important issue will remain to be seen.

2. Practice of safety pharmacology (ICH S7A)

Safety Pharmacology is “. . . those studies that investigate the potential undesirable pharmacodynamic effects of a substance on physiological functions in relationship to exposure in the therapeutic range and above. . .” (ICH S7A, Table 1). Three primary objectives are encompassed in these investigations.

(1) To provide a perspective of the potential pharmacodynamic risk posed to humans by exposure to a new therapeutic agent. This is accomplished through the pharmacodynamic characterization of the new drug on cardiovascular (Bunting & Siegl, 1994; Kinter & Johnson, 2003), respiratory (Murphy, 1994, 2002; Sarlo & Clark, 1995), and central (peripheral) nervous (Haggerty, 1991; Mattsson, Spencer, & Albee, 1996; Moser, 1991; Porsolt, Lemaire, Durmuller, & Roux, 2002; Ross, Mattsson, & Fix, 1998) systems (safety pharmacology core battery studies), and other major organ systems (supplemental studies; e.g., gastrointestinal Baldrick, Bamford, & Tattersall, 1998;

Kinter, 2003; Mojaverian, 1996 and renal, Chiu, 1994; Kinter, 2003) as appropriate based on concern for human safety.

(2) To investigate the underlying mechanism(s) of observed effects to refine and improve upon the integrated assessment of the risk posed by the drug when adverse findings have been noted in nonclinical or clinical investigations. These may be follow-up studies of the safety pharmacology core battery or the study of other major organ systems (supplemental studies) based on a potential clinical concern (Gad, 2004; Kinter & Dixon, 1995; Williams & Bass, 2003).

(3) To determine the temporal relationship between the pharmacodynamic responses noted with the test substance and the peak blood levels of parent drug and any major metabolites. This information will be used to identify the peak drug levels at the low-observed-effect level (minimal dose level tested that produces an effect; LOEL) and no-observed-effect level (maximum dose level tested without an effect; NOEL), the relationship between parent drug and/or major metabolite and the pharmacodynamic response, and whether the pharmacodynamic changes noted with the test material may be related to animal-specific metabolites. These data are critical to defining a margin of safety between the NOEL and the projection of plasma levels needed to achieve clinical efficacy. They also serve to define the human risk posed by exposure to the new drug (e.g., little risk if the response can be attributed to an animal-specific metabolite) and the possible timing of onset and recovery from any observed effects (Williams & Bass, 2003).

The safety pharmacology core battery and any supplemental studies deemed to be necessary to assure that human safety are to be conducted in advance of initial clinical trials (“first in human” studies) so that a new drug can progress safely into the clinical phases with an appropriate level of monitoring. In situations where the adverse effects are judged to be potentially serious, or when unexpected pharmacodynamic effects occur in humans, the next tier of testing, investigational safety pharmacology studies (e.g., follow up or supplemental studies), may be appropriate (ICH S7A; see Table 1).

The ICH S7A guideline has brought uniformity to the evaluations of new drugs for effects on organ functions, mandating with few exceptions, that all drug candidates will be evaluated in the safety pharmacology core battery studies and in follow up and supplemental as appropriate to assure human safety. The cardiovascular, respiratory, and central (peripheral) nervous system functions were selected for the safety pharmacology core battery based on the concern that an acute failure of these systems would pose an immediate hazard to human life. The examination of additional organ systems (e.g., gastrointestinal, renal, etc.) may also be appropriate based on a cause for concern for human safety. The experimental models, endpoints, and study designs chosen should be relevant to the prediction

of the potential human response. Preference is given to studying animals in the conscious versus the anesthetized states and in the unstressed/unrestrained versus stressed/restrained conditions, to the extent possible within modern Animal Welfare guidelines. The clinical route is the preferred route, unless otherwise justified, for example, intravenous rather than oral route to achieve higher blood levels of the parent drug, where oral bioavailability in the test species may be low. Data are collected for a period that has the potential to define the onset, duration, and recovery from possible pharmacodynamic effects. This data collection period would be initially based on the pharmacokinetic (or toxicokinetic) properties of a drug in the selected species and, at a minimum, encompass the time at which the maximum plasma concentrations of the parent drug and any major metabolites are achieved. The demonstration of reversibility/recovery from pharmacodynamic effects may be accomplished by waiting five or more half-lives before terminating the data collection. In the event that human-specific metabolites are detected in the early clinical phases, consideration would be given to nonclinical pharmacodynamic studies that would be appropriate to assure continued human safety.

3. Future of safety pharmacology

The future of safety pharmacology will depend, in part, upon the scientific and technological advances and regulatory challenges that envelop pharmaceutical development. With advances in molecular biology and biotechnology, which allows for the identification of new clinical targets, newer pharmaceutical agents are being identified that act at these novel molecular sites in an attempt to ameliorate the disease condition. Inherent in the novelty of new targets is the risk of unwanted effects that may or may not be detected with current techniques. The scientific challenge facing safety pharmacology is to keep pace, to adapt, and to incorporate new technologies in the evaluation of new drugs in nonclinical models and identifying the effects that pose a risk to human volunteers and patients. Recent examples include safety pharmacology’s embracement of modern electrophysiological techniques to evaluate the effects of new drugs on the ionic components of the cardiac action potential (Redfern et al., 2003), and telemetry techniques to permit the chronic monitoring of physiological functions in unstressed animals (Kinter & Johnson, 1999; Kramer & Kinter, 2003; Kramer, Mills, Kinter, & Brockway, 1998). Efforts continue to construct databases relating the similarities and differences between animal and human responses to pharmaceutical agents (Igarashi, Nakane, & Kitagawa, 1995; Olsen et al., 2000). As an example, nonclinical safety studies, including safety pharmacology studies, are typically conducted in normal, healthy, young adult or adult animals. However, these tests may not

appropriately detect specific responses in humans at other ages (e.g., neonates, adolescents, and geriatrics) or those with underlying chronic diseases (e.g., heart failure, renal failure, and type II diabetes), conditions which may alter the pharmacodynamic response to a drug. In some cases, animal models that overexpress or are deficient in the unique targets, or are otherwise manipulated to model the human pathophysiological conditions, may provide additional focus and sensitivity to detect and interpret the potential unwanted effects of new drugs in terms of human risk (Hondeghe, Carlsson, & Duker, 2001). The challenge is to identify nonclinical models that reflect the overall human pathophysiological condition and to incorporate these disease models along with traditional safety models into safety pharmacology paradigms to produce integrated and more accurate assessments of possible human risk. The conundrum posed by the introduction of new techniques and technologies in formulating a risk assessment is to improve and enhance the safe progression of new drugs to the marketplace, while preventing unnecessary delays (or discontinuances), based on nonclinical findings that are not relevant or interpretable in terms of clinical response or human risk.

The future of safety pharmacology is also intertwined with international regulatory guidelines such as ICH Topics S7A, S7B, and E14. The discipline is considered integral to the evolving regulatory strategies for safely accelerating the introduction of these drugs into the clinical phases [e.g., EMEA (CPMP), “Position Paper on Non-clinical Safety Studies to Support Clinical Trials with a Single Microdose” and the U.S. Food and Drug Administration, Screening Investigational New Drug Application]. Additionally, safety pharmacology is also considered important to newly emerging regulatory guidelines from U.S. Food and Drug Administration, such as the “Safety Evaluation of Pediatric Drug Products and Nonclinical Studies for development of Pharmaceutical Excipients.”

The introduction of pharmaceuticals into the environment is gaining the attention of both regulators and pharmaceutical industry (Calamari, 2003; Huggett, Khan, Foran, & Schlenk, 2003; Kopin et al., 2002). While this is not currently the subject of any international environmental guideline, the use of organ function endpoints may become an important component in bridging safety data collected in mammalian vertebrates (including humans) to aquatic species for purposes of the identification of relevant target species and organ functions and the design of specific environmental toxicology studies.

Safety pharmacology also faces significant challenges of attracting, training, and certifying investigators in integrative approaches to physiology, pharmacology, and toxicology to assure its promising new future. Thus, the answer to the future of safety pharmacology will be contained within the vision of its current and future leaders, the issues and concerns that they face, and the solutions to the important problems that they generate.

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