

SAFETY PHARMACOLOGY ASSESSMENT AND ASSOCIATED REGULATIONS

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Contents

1. Introduction
 2. Drug screening studies for assessing pharmacological activity
 3. Safety pharmacology studies in the context of regulatory guidelines
 4. Use of *in vitro* systems and *in vivo* models for safety pharmacology testing
 - 4.1. Core Battery Studies
 - 4.1.1. Cardiovascular System
 - 4.1.2. Respiratory System
 - 4.1.3. Central Nervous System
 - 4.2. Supplemental Studies
 - 4.2.1. Renal/Urinary System
 - 4.2.2. Gastro-intestinal System
 - 4.2.3. Autonomic Nervous System
 - 4.2.4. Immune System
 - 4.2.5. Dependency Potential
 - 4.2.6. Effects on Skeletal Muscle
 - 4.2.7. Endocrine System
 5. Concluding Remarks
- Glossary
Bibliography
Biographical Sketches

Summary

The aim of safety pharmacology studies is to identify adverse effects of new molecular entities (NMEs) and biological products that are administered to humans. They are done to evaluate adverse pharmacodynamic and/or pathophysiological effects. The safety pharmacology testing of NMEs aims to identify effects in biological systems that are unrelated to the intended primary pharmacological target. The results from such investigations form the basis for selecting NMEs for clinical development or for recommending the clinical and laboratory indices that should be monitored in the early phase clinical trials conducted during a new product development program. A set of core studies has been identified by regulatory agencies for regular investigations with all NMEs. Depending on the need, a second tier or supplemental studies may also be conducted selectively either prior to first administration to human, or in parallel with

early phase human studies provided there is no immediate concern for safety.

This chapter details selected current methodologies and focuses on the major organ systems, including the cardiovascular, respiratory and nervous systems, as well as the endocrine and immune systems.

1. Introduction

The word pharmacology is derived from the two Greek words, *pharmacon* (medicine) and *logos* (study). Pharmacology is the scientific study of the effects of therapeutically useful chemical agents and the underlying mechanisms by which they exert their biological responses. The term pharmacodynamics is sometimes used interchangeably with pharmacology, but it refers more specifically to the study, at molecular level, of the biochemical and physiological effects of therapeutic agents on cellular systems. A wide range of techniques is used in characterizing the pharmacological action of a new molecular entity (NME). They include biochemical, molecular and cellular methodologies. For regulatory purposes and in pharmaceutical development, three categories of pharmacological research are generally recognized, namely primary pharmacodynamics, secondary pharmacodynamics and safety pharmacology. Primary pharmacodynamic studies relate to the establishment of all aspects of the desired therapeutic effect as demonstrated in experimental *in vitro* and *in vivo* studies, i.e. primary action in the target system. Secondary pharmacodynamic investigations address the resultant action in the target system and effects that are outside the realms of primary therapeutic activity. Safety pharmacology investigations refer to pharmacodynamic effects in non-target systems that lead to side effects.

Safety pharmacology has evolved as an integrated discipline from the distinct fields of pharmacology, physiology and toxicology. The origins of safety pharmacology are based on observations that, organ functions can be toxicological targets in humans exposed to novel therapeutic agents. However, the drug effects on organ functions (unlike organ structures) are not readily detected by standard toxicological testing.

2. Drug Screening Studies for Assessing Pharmacological Activity

The need for a rapid and cost-effective method of addressing potential liabilities of drugs at the early discovery stage of lead selection and lead optimization has been referred to as ‘*in vitro* safety pharmacology profiling’ (*in vitro* SPP). It employs a large number of relatively inexpensive *in vitro* assays to do molecular target profiling of NMEs by *in vitro* SPP. By focusing on early hazard identification it can flag receptor-, enzyme-, transporter-, and channel-related liabilities. Interpretation of the data is aided by evaluation of results in conjunction with preliminary bioavailability and toxicity characteristics determined either *in vitro* or *in vivo*.

At the research stages and prior to administration to humans, NMEs are subjected to biological assays that explore molecular mechanisms of action and pharmacology.

The objective in these studies is to evaluate the potential for these compounds for use as therapeutic agents. A variety of testing methods can be used for this purpose and they

include: computer-assisted (*in-silico*) modeling, cloned receptors, cultured cells, isolated tissues or organs, specific enzyme inhibition or activation and animal models of human disease. They are intended to represent aspects of sub-molecular, molecular, cellular, organ or whole body components in a cascade of biological screening techniques. *In vitro* studies cover quantitative investigations at molecular and cellular levels providing for effective concentrations (EC_{50}) or inhibitory concentrations (IC_{50}) of an NME as an index of its potency. *In vivo* studies on the other hand, apply to in-life studies and are associated with animal experimentation. In applying these options, the use of validated assays and comparator (or reference) drugs will be of great benefit in reliably ranking the relative efficacy or activity.

In the design of studies, due consideration should be given to selection of sample size, use of controls and reference compounds. Analysis and interpretation of the results of pharmacodynamic activity are also usually considered in relation to the associated pharmacokinetics (drug disposition) and metabolism of the NME. If a potential exists for accumulation of a drug in plasma or tissues following repeated administration, safety pharmacology studies should consider a 7 to 14-day repeat dose protocol.

3. Safety Pharmacology Studies in the Context of Regulatory Guidelines

Whilst 'efficacy' studies in pharmacology deal with primary pharmacodynamic properties of a drug or NME, safety pharmacology studies are designed to investigate the potential undesirable pharmacodynamic effects of a substance on physiological functions in relation to exposure in the therapeutic range and above (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use [ICH] S7A Guidelines, 2000). The safety pharmacologist uses knowledge of physiology, biochemistry, anatomy, and cellular and molecular biology to evaluate and assess the safety profile of a new chemical or biological entity in a hierarchy of physiological systems necessary for survival. In these studies, functional indices of potential toxicity are measured (ICH S6 Guidelines, 1997). The doses selected for the studies may, therefore, have the potential to cause unwanted effects in non-target systems leading to side effects. In addition to the separately conducted toxicity assessments with new compounds, safety pharmacology studies provide important information to clinical investigators for potential acute adverse effects upon a number of body systems, such as cardiovascular, respiratory and central nervous system functions (Dixit, 2004). The ICH S7A Guidelines provide general information such as definitions, general principles, timing of studies, core battery of studies to be considered and compliance with Good Laboratory Practice. These concepts also apply to biotechnology-derived pharmaceuticals.

Cardiac side (adverse) effects of drugs, not intended for use in heart disease, have been recognized for sometime now and have become a main focus in selection of new products for pharmaceutical development. A complementary guideline has been developed that focuses on cardiac function effects of human pharmaceutical products and, more specifically, to assist in the evaluation of risk of ventricular repolarization-associated cardiac embarrassment (ICH S7B, 2005).

The afore-mentioned ICH guidelines have now been adopted by all major

pharmaceutical development and marketing territories of the world (USA, European Union and Japan) and are in use in the expectation that effects of an NME are investigated as part of the safety evaluation program prior to first administration to humans. This paper discusses the salient aspects of safety pharmacology studies that have been adopted by the pharmaceutical industry to address some of these concerns.

4. Use of *in vitro* Systems and *in vivo* Models for Safety Pharmacology Testing

Although the concept and importance of characterizing drug related non-target pharmacology that can lead to side effects has been recognized for a considerable period of time, it is the ICH initiative of the 1990s that has accelerated the thinking process and provided a consolidated position for the pharmaceutical industry to move forward on this front. A valuable compendium on aspects of safety pharmacology studies conducted at the present time, and a status update, have been published in the *Journal of Pharmacological and Toxicological Methods* (Pugsley, 2005). Another two publications relevant to this topic are the books by Gad (2004) and Vogel *et al.* (2006). They cover historical background information as well as providing a systemic approach to screening and designing safety pharmacology investigations, and also discuss the significance of integrating those endpoints into the wider context of drug disposition and pharmaceutical safety assessment.

Test systems, methods and standardized protocols for safety pharmacology studies are now on offer by Contract Research Organisations (CROs) at reasonable costs to a sponsor company screening NMEs. It would be up to a sponsor pharmaceutical company to decide exactly which tests are appropriate for the type of compound(s) in question. For *in vivo* studies, careful consideration should also be given to selection of animal species that would permit data comparison from other relevant studies within the program and the use of established methods and techniques that have been adequately validated in the laboratory conducting the studies. At least in part, these will help ensure quality standards and reproducibility of data and, therefore, a reliable extrapolation to the human situation. A further key consideration is that all safety pharmacology studies should be conducted under conditions of Good Laboratory Practice (GLP) and be officially certified as compliant with the regulations (US Food and Drug Administration [FDA], 1978; Organisation for Economic Cooperation and Development [OECD], 1998a; OECD, 2002; OECD, 2004). GLP is now an important part of the quality management of pharmaceutical laboratory data generation to provide a higher level of confidence in the reproducibility of data. They are a reflection of sound study management that ensures reliability and integrity of studies. In conducting these tests, it is usual to select a range of dose or concentration levels from clinically relevant to doses that are high but not toxic.

4.1. Core Battery Studies

Since undesirable pharmacodynamic effects to drugs may be related to a specific action on any of the non-primary target tissues or organs, in an extreme situation, it may be argued that safety pharmacology investigations should be conducted on all systems in the body. This would lead to a lengthy and expensive process of testing a new NME or a biological product. However, logistical and economic considerations are likely to dictate

a more rational approach and, therefore, the regulatory guidelines do recommend that a hierarchy of organ systems be developed, such as those that govern vital functions critical to life.

This has led to a general acceptance of cardiovascular, respiratory and central nervous system assessments as the important systems to be investigated as a ‘core battery’ of studies.

It would be expected that additional studies for investigating potential for affecting other systems would be identified as appropriate on a case by case basis for a given compound, dependent upon its chemical, biological and/or known toxicological characteristics. In the event of excluding investigations into a core battery study or system, these need to be scientifically justified (ICH S7A, 2000).

Further refinement by way of a schedule is offered by Redfern *et al.*, (2002) in their analysis of safety pharmacology studies, which suggests a ‘tiered approach’ to conducting these studies. In this step-wise approach, the *in vitro* studies would be positioned in the early stages of investigations of an NME (see Table 1).

<p>Lead Identification and Optimisation (>100 compounds)</p> <ul style="list-style-type: none"> - ‘In silico’ assessment - ‘Key’ receptors - ‘Key’ enzymes - ‘Key’ ion channels
<p>Candidate Drug Selection (2-4 compounds)</p> <ul style="list-style-type: none"> - ‘Receptogram’ partial profiling - Functional observational battery (FOB) - <i>In vitro</i> cardiac electrophysiology - Dog telemetry
<p>Candidate Drug Evaluation (pre-Phase 1) (1-2 compounds)</p> <ul style="list-style-type: none"> - Complete ‘receptogram’ profiling - Haemodynamics - Respiratory Function - Gastro-intestinal function - Tremor - Motor co-ordination - Learning and memory - Auditory Function - Locomotor activity - Startle reflex - Grip strength - Nociception - Electroencephalography - Anxiety test - Visual function

Table 1: Tiered approach to safety Pharmacology evaluation (Redfern *et al.*, 2002)

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Biographical Sketches

Dr Jega Iswaran received a PhD degree from the University of London, and the Membership (MRCPATH) and Fellowship (FRCPath) Diplomas of the Royal College of Pathologists (UK), specializing in toxicology and pathology. In the pharmaceutical industry, he has worked in various research and product development positions over a 30 year period. During his long tenure at ICI/Zeneca Pharmaceuticals, at the company's headquarters in England, he held senior positions of authority in the fields of safety pharmacology, toxicology and pathology and was actively associated with several international product development programs covering the therapeutic areas of cancer, endocrinology, infection, cardiovascular disease, CNS disease, gastrointestinal disease and respiratory disease. In this capacity, he also acted as company expert on matters of drug safety evaluation. Since 1996, he has lived in Australia and worked in the pharmaceuticals sector in Melbourne, first at CSL Bioplasma Limited and then as Development Director at Antisense Therapeutics limited. His current interests are in the areas of drug safety of antiviral agents.

Professor Jorma Ahokas is a pharmacologist/toxicologist by training. He received a PhD in Finland and did a postdoc as a Merck Sharp & Dohme Research Fellow in Clinical Pharmacology in the Department of Medicine, University of Queensland, followed by an Australian National Health & Research Council funded research post. After lectureships in the Department Pharmacology, University of Melbourne and RMIT, in 1991 he was appointed to a position of Foundation Professor in Toxicology at RMIT. It was the first full professorship in toxicology in Australia. Since 1998, he has been a Docent in toxicology at the University of Helsinki and since 1999 a visiting professor of toxicology at Toho University, Japan. His research has related to problems of drug and carcinogen metabolism as well as food and environmental toxicology. His current research interests relate to adverse effects of complementary remedies and their interactions with prescription medicines. He has been a consultant in areas of drug toxicity and environmental toxicology to industry and government bodies. Jorma Ahokas is a Professor of Toxicology, School of Medical Sciences, RMIT University.