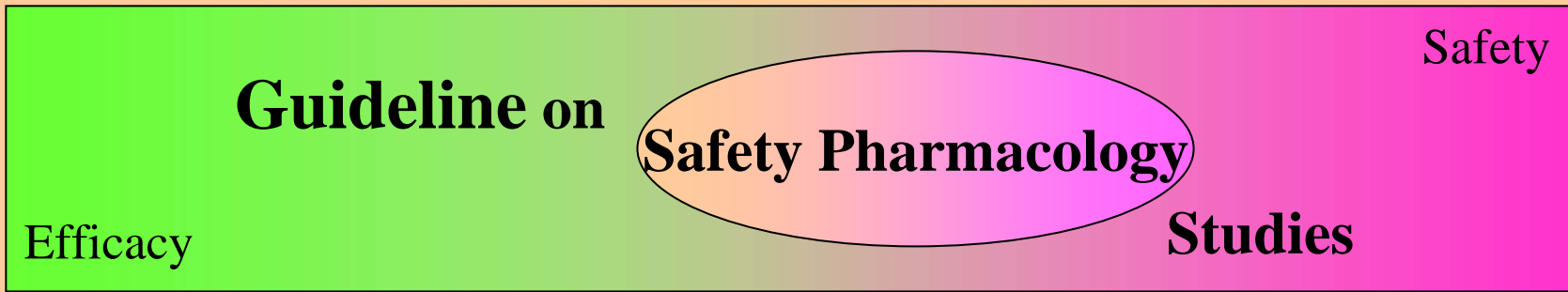


GUIDELINE ON SAFETY PHARMACOLOGY STUDIES FOR HUMAN PHARMACEUTICALS (S7A)

ICH S7 Expert Working Group

M. Hashimoto Ph.D.

Pharmacia



ICH-CTD
Definition:
Primary, Secondary
Pharmaco-dynamics
Safety Pharmacology

ICH-M3
Timing to Clinical
Studies

Step 1: Mar. 1999

Aug. 1999

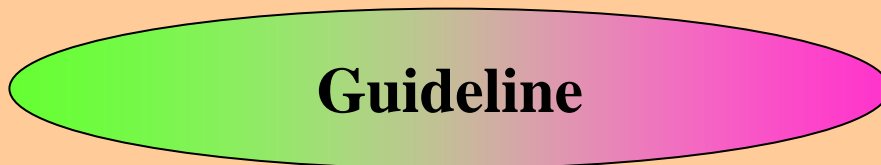
Oct. 1999

Step 2: Mar. 2000

Sep. 2000

Step 4: Nov. 2000

International Discussion
(Symposium on
General/Safety Pharmacology)



Hierarchical order
:Core
:Follow-up
:Supplemental
Application of GLP

Table of Content

1. INTRODUCTION

1.1 Objectives Of The Guideline

1.2 Background

1.3 Scope Of The Guideline

1.4 General Principle

1.5 Definition Of Safety Pharmacology

2. Guideline

2.1 Objectives Of Studies

2.2 General Consideration In Selection/Design

2.3 Test Systems

2.4 Dose Levels/Concentrations

2.5 Duration Of Studies

2.6 Metabolites, Isomers, Finished Products

2.7 Core Battery

2.8 Follow-up And Supplemental Studies

2.9 Conditions Under Which Studies Are Not Necessary

2.10 Timing In Relation To Clinical Development

2.11 Application Of GLP

3. Notes (Note 3 : QT issues, S7B)

Major Points of Guideline

- **Definition**
- **Rational Approach**
- **Core Battery, Follow-up and Supplemental Safety Pharmacology Studies Based on Hierarchical Order of Organ Systems**
- **Investigation in Relation to Systemic Exposure**
- **Considerations for Dose Selection**
- **Timing in Relation to Clinical Development**
- **GLP Application**

Definition of SP

- **Studies that investigate the potential undesirable pharmacodynamic effects on physiological functions **in relation to exposure in the therapeutic range and above****
- **Primary: Studies on the mode of action and or effects in relation to the desired therapeutic target**
- **Secondary: Studies on the mode of action and/or effects not related to the desired therapeutic target**

Scope of Guideline

New chemical entities

Biotechnology-derived products

Marketed pharmaceuticals when appropriate

General SP Principles

- **Rational Approach** in Design and Conduct Based on Pharmaceutical's Properties and Uses
- **Scientifically Valid Methods**
- Use of **New Technologies** and **Methodologies** is Encouraged
- Potential to **Incorporate SP Endpoints** into Toxicology, Kinetics, Clinical studies etc.

Objectives of SP Studies

- **Identify** undesirable pharmacodynamic properties relevant to human safety
- **Evaluate** adverse pharmacodynamic effects observed in toxicology and/or clinical studies
- **Investigate** mechanisms of adverse pharmacodynamic effects

Route(s) of Administration

- **Clinical route** preferred
- **Exposure** achieved **similar to or greater** than in humans
- If clinical use involves multiple routes, consider more than one route

Duration of Studies

- **Generally single dose**
- **Consider repeat dose when:**
 - **PD effect only after a certain duration**
 - **Concerns from repeat dose non-clinical studies and human use**

Safety Pharmacology Core Battery

- **Focus on Vital Functions**
 - **Central Nervous System**
 - **Cardiovascular System**
 - **Respiratory System**

Safety Pharmacology Core Battery (continued)

Central Nervous System

- **Motor activity**
 - **Behavioral changes**
 - **Coordination**
 - **Sensory/motor reflex responses**
 - **Body temperature.**
- (e.g. FOB, Irwin's test, Neurotoxicity testing)**

Safety Pharmacology Core Battery (continued)

Cardiovascular System

- Blood pressure, heart rate, ECGs.
- Consider in vivo, in vitro and/or ex vivo evaluations including methods for repolarization and conductance abnormalities
(S7B Guideline will follow: Panel discussion)

Safety Pharmacology Core Battery (continued)

Respiratory System

- **Clinical observation alone generally not adequate**
- **Quantitative measurement of respiratory rate and other measures (tidal volume or hemoglobin oxygen saturation)**

Follow-up and Supplemental SP Studies

Consider when:

- Adverse effects suspected based on the **pharmacological properties and chemical class**
- **Concerns** from the safety pharmacology core battery, clinical trials, pharmacovigilance, experimental in vitro or in vivo studies, or from literature reports

Follow-up Studies

- **Case-by-case**
- Provide **a greater depth of understanding**
- List provided **not comprehensive or prescriptive**
- In some cases more appropriate to address effects in **other non-clinical and/or clinical studies**

Supplemental Studies

- **Other organ systems not addressed by core battery**
 - **Renal/Urinary System**
 - **Autonomic Nervous System**
 - **Gastrointestinal System**

Conditions Under Which Studies Are Not Necessary

- **Some locally applied agents (e.g. dermal or ocular)**
- **Some cytotoxic agents for treatment of end-stage cancer patients**
- **Some biotechnology-derived products**
- **Some other cases based on PK and PD**

Timing in Relation to Clinical Development

- **Prior to first administration in humans**

Core battery

Follow-up and supplemental based on a cause for concern

- **During clinical trial**

To clarify observed undesirable effects in animals and humans

- **Before approval**

Supplemental studies unless not warranted.

- Justify

- SP endpoints covered in other studies

S7A Panel Discussion

Dr. J. DeGeorge: Dose Selection

**Dr. J. Moe: Metabolites, Isomers And
Finished Products**

Dr. K. Fujimori: Good Laboratory Practice

**Dr. K. Olejniczak: Future Activities : S7B
QT/Torsade**

Dose Levels In Vivo

- Define dose-response
- **Include and exceed** primary PD or therapeutic range
- Absent adverse effect on SP parameter, use dose producing **moderate** adverse effects in this or in other (toxicology) studies of similar route and duration

Metabolites

- **Consider SP Studies When Metabolites:**
 - Achieve systemic exposure in humans
 - Are absent or at low concentration in animals
 - Contribute to pharmacological activity
- **In Vitro Test Systems Can Be Used Based On Practical Considerations**

Isomers and Finished Products

- **Consider SP Testing Of:**
 - Individual isomers in an isomeric mixture
 - New formulations that substantially alter PK or PD of finished product

Application of GLP

Safety Pharmacology Studies = Safety Studies

- **NOT GLP**

- Primary PD Studies
- Secondary PD when not pivotal to safety

- **Ordinarily GLP**

- Core battery
- SP endpoints from toxicology studies
- Secondary PD studies when pivotal *

- **GLP to the greatest extent feasible**

- Supplemental, Follow-up

* When results significantly contribute to safety evaluation for human potential adverse effects

Implementation of GLP

- **Exceptions**

- Unique design
- Practical consideration

- **Data quality and integrity**

In the absence of formal adherence to the Principle of GLP

- **Ensure study reconstruction**
- **Provide rationale**
- **Explain impact**

S7B

Non-clinical Approaches for Predicting Torsade de Pointes

Objectives:

To outline available nonclinical methodologies for assessment of potential ventricular tachyarrhythmia

To discuss the advantages and disadvantages of the systems and models.

S7B

Non-clinical Approaches for Predicting Torsade de Pointes

Current state of guidance

CPMP "Points to Consider" document

Publications

Systems/Models available:

Advantages and Limitations of each

- Heterologous expression systems
- Disaggregated cells
- Isolated tissue
- Isolated intact heart (Langendorff)
- Intact animal (e.g., Guinea pig, rabbit, dog, pig)

General Consideration in Selection and Design

- **Therapeutic class** (e.g. proarrhythmia of antiarrhythmic agents)
- **Members of the chemical or therapeutic class** but independent of primary PD effects (e.g. anti-psychotics and QT prolongation)
- Ligand binding or enzyme assay
- Results from Previous SP, secondary PD, tox studies, or from human use
- **Hierarchy**: life-supporting system (CNS, CVS, Respiratory)

Other organ systems when considering factors, e.g., clinical trial or patient population