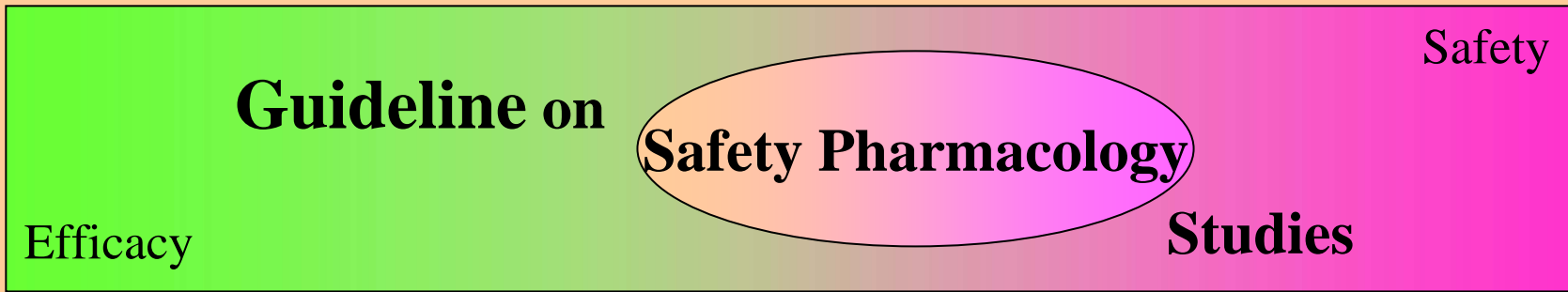


# **GUIDELINE ON SAFETY PHARMACOLOGY STUDIES FOR HUMAN PHARMACEUTICALS (S7A)**

ICH S7 Expert Working Group

M. Hashimoto Ph.D.

Pharmacia



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

**Step 1: Mar. 1999**

**Aug. 1999**

**Oct. 1999**

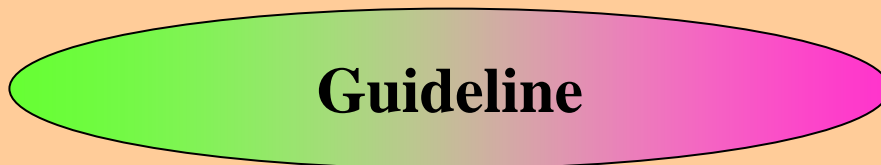
**International Discussion**  
 (Symposium on  
 (**General/Safety** Pharmacology))

**Step 2: Mar. 2000**

**Sep. 2000**

**ICH-M3**  
**Timing to Clinical**  
**Studies**

**Step 4: Nov. 2000**



**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