GUIDELINE ON SAFETY PHARMACOLOGY STUDIES FOR HUMAN PHARMACEUTICALS (S7A)

ICH S7 Expert Working Group

M. Hashimoto Ph.D.

Pharmacia

ICH-5 November 10, 2000

Safety

Guideline on Safety Pharmacology Studies

Efficacy

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)

Guideline

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

Table of Content

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 ICH-5 November 10, 2000

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, Resiratory)**

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