GUIDELINE ON SAFETY PHARMACOLOGY STUDIES FOR HUMAN PHARMACEUTICALS (S7A)

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ICH-5 November 10, 2000
ICH-5 November 10, 2000

Safety Pharmacology

International Discussion
(Symposium on (General/Safety Pharmacology)

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

ICH-M3
Timing to Clinical Studies

Guideline on
Safety Pharmacology

Efficacy

Step 1: Mar. 1999
Aug. 1999
Oct. 1999

Step 2: Mar. 2000
Sep. 2000

Step 4: Nov. 2000

Guideline

International Discussion
(Symposium on (General/Safety Pharmacology)

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

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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
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.
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