【S-9】

Safety Pharmacology Studies in Korea

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The Korea Food & Drug Administration (KFDA) has been reorganized on September 30, 2005 to maximize it's specialty and efficiency. We, Pharmaceutical Headquarter, one of the six Headquarters in KFDA, review IND and NDA documents for approval of manufactured or imported drugs. Recently, we notified the revised draft of "Regulation for review of safety and efficacy of drugs". In the revised draft, the safety pharmacology study is added in the animal pharmacology, although we have reviewed the safety pharmacology data before the notification of revised draft of regulation. Until now, we reviewed the safety pharmacology data according to the ICH guidelines because we don't have our own guidelines. So, In 2003, the National Institute of Toxicological Research (NITR) have started study to establish the draft of the guidelines on safety pharmacology and it will be notified after a while. We will issue the certificate to the GLP facilities for safety pharmacology study item, after revising of the "Regulation for review of safety and efficacy of drugs" and " KFDA GLP guidelines" and enacting the "Guidelines on safety pharmacology".

Safety Pharmacology in Korea

Korea Food & Drug Administration

Young-Ok Kim

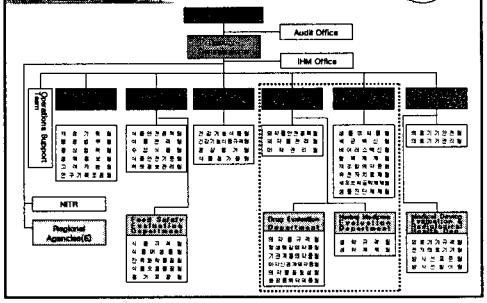
Contents

KFDA

1. Organization & Review Process
2. *Current Status*
3. *Guideline on Safety Pharmacology Studies*
4. *Review on the Data of Safety Pharmacology Studies*
5. *Future Plans*

Organization

KFDA



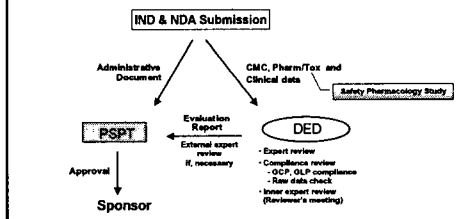
Main Functions

KFDA

Chemistry and Cardiovascular Drug Team	
Antibiotics and Oncology Drug Team	
Gastrointestinal, Urinary and Metabolic Drug Team	
Narcotic and Neuropharmacological Drug Team	
Bioequivalence Team	
Cosmetics and Quasi-drug Team	

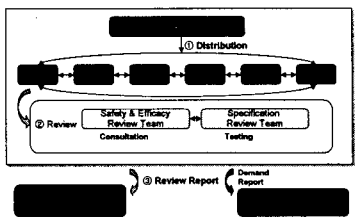
Review Process

KFDA



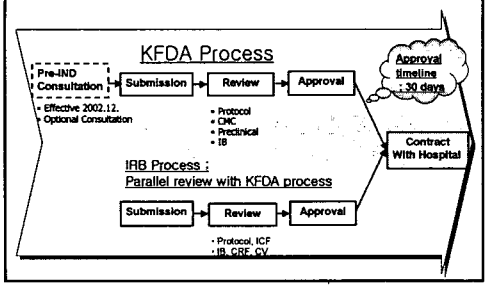
Review Process

KFDA



IND Process

KFDA



KFDA

1. *Organization & Review Process*

2. Current Status

3. *Guideline on Safety Pharmacology Studies*
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Current Status

KFDA

- **Regulations**
  - **1997. 7. 11 : Guideline on General Pharmacology Studies (Korea Food and Drug Safety Headquarter Notification 1997-2)**
  - **1998. 5. 29 : Guideline on General Pharmacology Studies (KFDA Notofication 1998-2)**

Current Status

KFDA

- **Draft of Guideline**
  - **2003~2004 : Study on Safety Pharmacology Studies (NITR)**
  - **2004 : Guidance on Safety Pharmacology Studies**

Current Status

KFDA

- **Now : Review**
  - **Nothing is about Safety Pharmacology Studies in the regulations for IND /NDA**
  - **ICH guideline (S7A)**

KFDA

1. *Organization & Review Process*
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Guideline KFDA

Safety Pharmacology

- Non-Clinical study
- Dose : More than therapeutic dose levels
- Evaluation : Potential Undesirable Pharmacodynamic Effects
- GLP
- Test systems

Guideline KFDA

Contents : 15 Articles

- Objectives
- Definition
- Scope
- General Principle
- Subject of Evaluation
- General Consideration
- Test System
- Dose Levels
- Duration of Studies
- Test Substance
- Safety Pharmacology Core Battery
- Follow-up & Supplemental Safety Pharmacology Studies
- Exemption
- Timing
- Application of GLP

Guideline KFDA

Objective of Guideline

- Enforcement Regulation of the Pharmaceutical Affairs Act Article 27
- Protecting trial subjects & patients from adverse drug reaction
- Protecting too much using of Animals & Resources
  - General Principle, Test Method, etc. (Confidence)
  - Safety Evaluation of Pharmaceutical products

Guideline KFDA

Definition

Safety pharmacology studies are defined as those studies that investigate the potential undesirable pharmacodynamic effcets of a substance on physiological functions in relation to exposure in the therapeutic range and above.

Guideline KFDA

Scope of Guideline

1. New Chemical Entities
2. Biotechnology-derived products for human use
3. Marked pharmaceuticals
   - Adverse clinical events
   - New Patient population or New Route of Administration

Guideline KFDA

General Principle

1. Rational Methods
   - Internationally recognized methods
   - Scientifically valid methods
2. Safety Pharmacology Studies, Design
   - Properties of test substances, Intended Use
3. New technlogies & mehtodologies : Scientific principle
4. Others
   - Toxicology, Kinetic, Clinical studies

Guideline KFDA

Objective of Safety Pharmacology Studies

1. To identify undesirable pharmacodynamic properties of a substance that may have relevance to it's human safety
2. To evaluate adverse pharmacodynamic and/or pathophysiological effects of a substance observed in toxicology and/or clinical studies
3. To investigate the mechanism of the adverse pharmacodynamic effects observed and/or suspected

Guideline KFDA

General Cosiderations in Selection & Design

1. Effects related to the vary depending on the specific properties of each test substance(mechanism of action may suggest specific adverse effects)
2. Adverse effects associated with members of the chemical or therapeutic class
3. Ligand binding or enzyme assay data suggesting a potential for adverse effects
4. Results from safety pharmacology studies, secondary pharmacodynamic studies, toxicity studies, or from human use

※ Insufficient information during early development : more general approach

Guideline KFDA

Test Systems

1. General Considerations

- Pharmacodynamic responsiveness of Model, Pharmacokinetic Profile
- Species, strain, gender, age of the experimental animals,
- Susceptibility, Sensitivity, reproducibility of test systems
- Background data on the substance
- Data from humans(*in vitro metabolism*)

2. Time points

Pharmacodynamic & Pharmacokinetic consideration

3. Test Systems

***In vivo, ex vivo, in vitro* model (rational reason for selection)**

Guideline KFDA

Test Systems

Ex vivo Isolated organs, Tissues, Cell cultures, Cellular fragments, Receptors Subcellular organells, Ion Channels, Transporters, Enzymes

In vitro Supportive studies

- Profile of the activity of the substance
- Investigating the mechanism of effects observed *In vivo*

In vivo Unanesthetized animals(avoidance of discomfort or pain)

- Telemetry etc.

Guideline KFDA

Test Systems

- Sample size :
  - Biologically significant effects
  - Size of the biological effects
- Control Group : Negative & Positive control
  - Well characterized *In vivo* test system : Positive control(X)
  - Exclusion of controls : Justification
- Route of Administration : expected clinical route, more than one route
- Dose levels : Dose-Response(onset & duration of response), highest tested dose, limit dose

Guideline KFDA

Duration of Studies

- Single dose toxicity
- Rational duration
  - Pharmacodynamic effects (after certain duration of treatment)
  - Pharmacodynamic effects (only repeated dose toxicity)
  - Safety Pharmacological effect

Guideline KFDA

Test Substance

1. Parent compound, Major metabolites
   a. Major metabolites : parent compound
   b. Evaluation of influence of metabolites
   c. Active metabolites
   d. Metabolites(*in vitro*)
2. Isomers
   Individual isomers(*in vitro or in vivo test*)
3. Finished Products
   Formulations that substantially alter the PK and/or PD

Guideline KFDA

Safety Pharmacology Studies

Safety Pharmacology Core Battery
: to investigate the effects of the test substance on vital function

Follow up Study for Safety Pharamcology Core Battery
: to provide a greate depth of understanding than that provided by the core battery on vital function

Supplemental Safety Pharmacology Studies
: to evaluate potential adverse pharmacodynamic effects on organ system functions

Guideline KFDA

Exemption

1. Local Applied Agents :
   Pharmacological Chracterization,
   Low Systemic exposure or distribution (Dermal, Occular)
2. Cytotoxic Agents :
   Treatment of end-stage cancer patients (exception of New mechanism)
3. Biotechnolgy-Derived Products : Specific receptor
   Sufficient evaluation of toxicity or pharmacodynamics(Safety pharmacology)
   (if novel therapeutic class and/or not specificity of receptor)
4. New Salt : New Salt having similar PK and PD

Guideline KFDA

Timing

- Safety Pharmacology Core Battery :
  - Prior to First Administration in Human
  - Adequate Follow-up Study & Supplemental Study
  - Toxicity Data(Evaluation of Safety Pharmacology)
- Follow-up Study :
  - During Clinical Development
  - To clarify adverse effects in animals & humans

❖ Safety Pharmacology Studies :
  - Before Approval
  - Adequate reason if not necessary

Guideline KFDA

Application of GLP

- GLP Compliance
  - Safety Pharmacology Studies(USA, Japane, EU)
  - Safety Pharmacology Core Battery
  - Safety Pharmacology Studies(Toxicity)
  - Follow-up & Supplemental Safety Pharmacology Studies
- GLP Non-compliance
  - Impossibility of GLP Compliance (speciality of test system)
    : to ensure the confidence by the documents, adequate reason
  - Primary & Secondary Pharmacodynamic Study
    (Influence on evaluation of adverse drug reaction:GLP Compliance)

KFDA

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ICH KFDA

2.6.2.4 Safety Pharmacology

In some cases, secondary pharmacodynamic studies can contri bute to the safety evaluation when they predict or assess potenti al adverse effect(s) in humans. In such cases, these secondary pharmacodynamic studies should be considered along with safe ty pharmacology studies.

ICH KFDA

The Nonclinical Tabulated Summaries – Templates

2.6.3 Pharmacology
- 2.6.3.1 Pharmacology: Overview
- 2.6.3.2 Primary Pharmacodynamics
- 2.6.3.3 Secondary Pharmacodynamics
- 2.6.3.4 Safety Pharmacology
- 2.6.3.5 Pharmacodynamic Drug Interactions

ICH KFDA

2.6.3.1 Pharmacology

	Overview		Test Article:		
Type of Study	Test System	Method of Administration	Testing Facility	Study Number	Location Vol. Section
Primary Pharmacodynamics					
Secondary Pharmacodynamics					
Safety Pharmacology					
Pharmacodynamics Drug Interactions					

ICH KFDA

2.6.3.4 Safety Pharmacology

								Test Article :
Organ Systems Evaluated	Species/ Strain	Method of Admin.	Doses (mg/kg)	Gender and No. Per Group	Noteworthy Findings	GLP Compliance	Study Number

Review KFDA

일반약리시험자료 요약서

시험항목	자료유무	주의점	주의결과	참 조	검토의견
일반행동에 미치는 영향	R/F				
중추신경계에 미치는 영향-자발운동량					
중추신경계에 미치는 영향-수면					
중추신경계에 미치는 영향-운동협조성					
중추신경계에 미치는 영향-경련					
중추신경계에 미치는 영향-통증					
중추신경계에 미치는 영향-체온					
자율신경계에 미치는 영향					
호흡기계에 미치는 영향					
순환기계에 미치는 영향					
소화기계에 미치는 영향					
비뇨기계에 미치는 영향					
기타에 미치는 영향					

KFDA

1. *Organization & Review Process*
2. *Curent Status*
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5. Future Plans

Future Plans KFDA

1. 2005 : Revising the regulations

(Guideline on Safety Pharmacology Studies)

- Regulation for Review of Safety & Efficacy of Drugs
- GLP Guideline
- Regulation for clinical study approval

2. 2006 : To certify the test facilities

Future Plans KFDA

Revision of GLP Guideline

비임상시험기관운영규정(제3조관련)

I. 총 칙

1. 목적

비임상시험기준(Good Laboratory Practice, GLP)은.....

2. 범 위

비임상시험기관운영은.....비임상시험은 단회투여독성시험, 반복투여독성시험, 유전독성시험, 생식·발생독성시험, 발암성시험, 안전성약리시험, 기타 특성시험 및 임부수탁시험 등에 적용된다.

Future Plans KFDA

Revision of GLP Guideline

[별표 2] 비임상시험기관지정규정(제4조관련)

1. 목적

2. 지정신청사항 제출

고시 제4조의 규정에 .....제출하여야 한다.

(1) 지정신청기관의 시설현황내역서

(2) 지정신청기관의 운영현황내역서

(3) 각 시험항목별 질적수준서

지정신청서 작성서 시험항목은 다음과 같다.

가. 단회투여독성시험

- 생지표시/비생체지표/병장유 분리해서 지정, - 흡입독성시험 지정의 경우, 별도 기술

나. 반복투여독성시험

- 생지표시/비생체지표/병장유 분리해서 지정, - 흡입독성시험 지정의 경우, 별도 기술

다. 유전독성시험

- 복귀돌연변이시험, - 염색체이상시험, - 소핵시험, - 기타

라. 생식·발생독성시험

- 수태능 및 초기배발생시험, - 출생전후발생 및 모체기능시험, - 배태자발생시험

마. 발암성시험

바. 안전성약리시험

- 중추신경계에 대한 영향 평가시험
- 심혈관계에 대한 영향 평가시험
- 호흡기계에 대한 영향 평가시험 - 기타

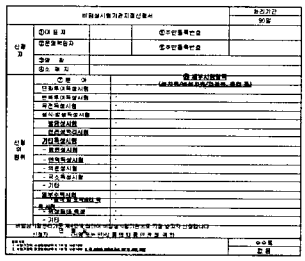
사. 기타독성시험

- 특성표시화, - 면역독성시험, - 국소독성시험, - 의존성시험, - 광독성시험
- 광감작성시험 등

아. 임부 수탁시험 : - 혈액 및 조직병리학적 시험, - 독성동태 측정, - 기타

Future Plans KFDA

Revision of GLP Guideline



Future Plans KFDA

Regulation for Review of Safety & Efficacy of Drugs

제5조(의약품등의 제출자료의 범위) ①.....

5. 악리작용에 관한 자료

가. 효력시험자료

나. 일반악리시험자료 또는 안전성약리시험자료

다. 흡수, 분포, 대사 및 배설시험자료

Future Plans KFDA

Regulation for Review of Safety & Efficacy of Drugs

제6조(제출자료의 요건) ①.....

5. 악리작용에 관한 자료

가. (현행과 같음)

나. 시험방법 (현행과 같음)

1) 효력시험자료 : 상사대상 효능을 포함한 효력을 뒷받침하는 악리작용에 관한 시험자료로서 효과 발현의 작용 기전이 포함된 자료

2) 악리시험자료

가) 일반악리시험자료 : (현행과 같음)

나) 안전성악리시험자료 : 의약품을 치료용량 범위 또는 그 이상의 용량으로 노출시켰을 경우 생리적 기능에 나타날 수 있는 비합리하지 않은 잠재적 약력학적 효과를 평가하기 위한 자료

3) 흡수·분포·대사 및 배설시험자료 : (현행과 같음)

Future Plans KFDA

Regulation for Review of Safety & Efficacy of Drugs

제7조(제출자료의 면제등) ①..

④ 2개국 이상에서 판매되는 의약외품의 경우에는 독성시험자료를 면제할 수 있으며, 살충제의 경우에는 일반약리시험자료 또는 안전성약리시험자료와 흡수•분포•대사•배설에 관한 자료를 추가로 면제할 수 있다

Future Plans KFDA

[별표 1] 의약품의 종류 및 제출자료의 범위

구분 \ 제출자료 (자료번호)	1	2 가	2 나	2 다	3 가	3 나	3 다	4 가	4 나	4 다	4 라	4 마	4 바	5 가	5 나	5 다	6 가	6 나	7	8	비고
1. 새로운 활성성분 함유의약품 (신약)	○	○	○	○	○	○	○	○	○	○	○	△	△	[illegible]	○	[illegible]	○	○	○	○	주2
2. 활성성분은 동일하나 [illegible] 새로운 의약품	○	○	○	○	○	○	×	△	△	△	△	△	△	[illegible]	△	[illegible]	○	×	○	○	주3
3. 새로운 이성체를 함유(분리)한 의약품	○	○	○	○	○	○	×	○	△	△	△	△	△	[illegible]	△	[illegible]	○	×	○	○	주4
4. 새로운 조성 의약품	○	×	×	○	○	○	×	○	△	×	×	×	△	[illegible]	△	[illegible]	○	×	○	○	주5
5. 새로운 투여경로 의약품	○	×	×	○	○	○	×	○	△	×	△	△	△	[illegible]	△	[illegible]	○	×	○	○	주2 주6
6. 새로운 효능 의약품	○	×	×	×	×	×	×	×	×	×	×	×	×	[illegible]	×	[illegible]	○	×	○	○	
7. 새로운 용법·용량 의약품	○	×	×	×	×	×	×	×	×	×	×	×	×	[illegible]	×	[illegible]	○	×	○	○	주7
8. 새로운 기원의 효소, 효모, 균주제 (약리학적으로 기원 동일)	○	○	○	○	○	○	×	○	×	×	×	×	×	[illegible]	△	[illegible]	△	×	○	○	
9. 방사성의약품 (체외진단용의약품 제외)	○	○	○	○	○	○	○	△	×	×	×	×	△	[illegible]	△	[illegible]	○	×	○	○	
10. 새로운 제형 (동일투여경로)	○	×	×	○	○	○	×	아래 "별표"에 의함											○	○	

약리작용에 관한 자료
안전성약리시험자료

Future Plans KFDA

[illegible]

Future Plans KFDA

II 살충제
II-1. 신물질 함유 살충제

구분 \ 제출자료	1	2	3 가	3 나	4 가	4 나	4 다	4 라	4 마	4 바	4 사	5 가	5 나	5 다	6	7
1. 유제	○	○	○	○	○	△	○	○	△	△	△	○	○	○	○	○
2. 에어로솔제	○	○	○	○	△	△	○	○	△	○	○	○	○	○	○	○
3. 유인살충제	○	○	○	○	○	△	○	○	△	×	×	○	△	○	○	○
4. 가피제	○	○	○	○	○	○	○	○	△	△	○	○	○	○	○	○
5. 증산제	○	○	○	○	○	△	○	○	△	○	×	○	○	○	○	○
6. 기타 제형	○	○	○	○	△	△	△	△	△	△	△	○	△	○	○	○

Future Plans KFDA

Regulation for clinical study approval

제4조(제출자료의 범위) 임상시험을 실시하고자 하는 자는 임상시험계획 승인을 위하여 다음 각호의 자료를 제출하여야 하며, 임상시험계획의 특성에 따라 제출하여야 하는 자료의 범위는 별표와 같다. 다만, 임상시험계획 변경승인을 신청하는 경우에는 변경에 필요한 해당자료만을 제출한다

1. 개발계획
2. 서론
3. 구조결정, 물리화학적 및 생물학적성질에 관한자료(위약포함)
4. 비임상시험성적에 관한 자료
   가. 효력 및 일반약리 또는 안전성약리시험자료
   나. 흡수,분포,대사, 배설에 관한 자료
   다. 독성에 관한 자료
   (1) 단회투여독성시험자료
   (2) 반복투여독성시험자료
   (3) 유전독성시험자료
   (4) 생식발생독성시험자료
   (5) 발암성시험자료
   (6) 시험물질특성에 따른 기타독성시험자료(국소독성, 의존성, 항원성 및 면역독성 등)
5. 임상시험성적에 관한 자료(제출가능한 경우)
6. 임상시험계획서
7. 근거자료목록
8. 임상시험자자료집

Safety Pharmacology in Korea

Thank You

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