Klinische Studien: Perspektive aus der Praxis

Forum Technische Entwicklung, Haftpflicht und Versicherung
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Agenda

- What is a clinical trial?
- Drug development phases
- Key Players
- Relevant regulations
- Clinical Trial process / documentation
- Introduction to Indemnity and Insurance

The Package Insert (Product Label)

ADME

Special Popⁿ

Age

MoA

Renal

PK

Hepatic

Gender

DDI

PD

QTc

Geriatric

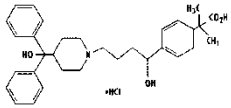
Pediatric

Dosing

Overdose

DESCRIPTION

Fexofenadine hydrochloride, the active ingredient of ALLEGRA®, is a histamine H_1-receptor antagonist with the chemical name (±)-4-[1-hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-butyl]-α , α-dimethyl benzeneacetic acid hydrochloride. It has the following chemical structure:



The molecular weight is 538.13 and the empirical formula is $C_{32}H_{39}NO_4$•HCl. Fexofenadine hydrochloride is a white to off-white crystalline powder. It is freely soluble in methanol and ethanol, slightly soluble in chloroform and water, and insoluble in hexane. Fexofenadine hydrochloride is a racemate and exists as a zwitterion in aqueous media at physiological pH.

ALLEGRA is administered orally. Each fexofenadine hydrochloride tablet for oral administration contains the following excipients: microcrystalline cellulose, and pregelatinized starch. The printing ink on the tablet shell is made from gelatin, iron oxide, carbon dioxide, sodium lauryl sulfate, titanium dioxide, and other ingredients.

CLINICAL PHARMACOLOGY

Mechanism of Action

Fexofenadine, a metabolite of terfenadine, is an antihistamine with selective peripheral H_1-receptor antagonist activity. [illegible] induced bronchospasm, histamine release [illegible]. In laboratory animals, [illegible] adrenergic-receptor blocking activity. Moreover, no sedative or [illegible] central nervous system effects were observed in radiolabeled tissue distribution studies, which indicated that fexofenadine does not cross the blood-brain barrier.

Pharmacokinetics

Fexofenadine hydrochloride was rapidly absorbed following oral administration of a single dose of two 60-mg capsules to healthy male volunteers with a mean time to maximum plasma concentration occurring at 2.6 hours postdose. After administration of a single 60-mg dose as solution to healthy subjects, the mean [illegible] for 10 doses). Fexofenadine pharmacokinetics were linear for oral doses up to 120 mg twice daily. Although the absolute bioavailability of fexofenadine hydrochloride capsules is unknown, the capsules are bioequivalent to an oral solution. The mean elimination half-life of fexofenadine was 14.4 hours following administration of 60 mg, twice daily, to steady-state in normal volunteers.

Human mass balance studies documented a recovery of approximately 80% and 11% of the [^{14}C] fexofenadine hydrochloride dose in the feces and urine, respectively. Approximately 5% of the total dose was metabolized. Because the absolute bioavailability of fexofenadine hydrochloride has not been established, it is unknown if the fecal component represents unabsorbed drug or the result of biliary excretion.

The pharmacokinetics of fexofenadine hydrochloride in seasonal allergic rhinitis patients were similar to those in [illegible]. Fexofenadine plasma concentrations [illegible] between adolescent (12 [illegible]) and adult patients.

Fexofenadine is 60% to 70% bound to plasma proteins, primarily albumin and [illegible] glycoprotein.

Special Populations

Special population pharmacokinetics (for age and renal and hepatic impairment), obtained after a single dose of 80 mg fexofenadine hydrochloride, were compared to those from normal volunteers in a separate study of similar design. Mean body weights were relatively uniform across groups. These special population patients were older than the healthy, young volunteers, so the age effect may be confounding the pharmacokinetic differences observed in some special populations.

Effect of Age. In older ≥ 65 years old), peak plasma levels of fexofenadine were 99% greater than those observed in normal volunteers (<65 years old). Mean elimination half-lives were similar to those observed in normal volunteers.

Renally Impaired. [illegible] clearance 41-80 mL/min) to severe (creatinine clearance 11-40 mL/min) renal impairment, peak plasma levels of fexofenadine were 87% and 111% greater, respectively, and mean elimination half-lives were 59% and 72% longer, respectively, than observed in normal volunteers. Peak plasma levels in patients on dialysis (creatinine clearance ≤ 10 mL/min) were 82% greater and half-life was 31 hours longer than observed in normal volunteers. Based on increases in bioavailability and half-life, a 60-mg once daily is recommended in patients with decreased renal function. (See DOSAGE AND ADMINISTRATION.)

Hepatically Impaired. The pharmacokinetics of fexofenadine hydrochloride in patients with hepatic disease did not differ substantially from that observed in healthy subjects.

Effect of Gender. Across several trials, no clinically significant gender-related differences were observed in the pharmacokinetics of fexofenadine.

Pharmacodynamics

Wheal and Flare. [illegible] histamine skin wheal and flare studies following single [illegible] daily doses of 20 mg and 40 mg fexofenadine hydrochloride demonstrated that the drug [illegible] effect by 1 hour, achieves [illegible] hours, and an effect is still [illegible] was no evidence of tolerance [illegible] 28 days of dosing.

Effects on QTc. In dogs, (10 mg/kg/day, orally for 5 days) and [illegible] (10 mg/kg, intravenously over one hour) fexofenadine [illegible] plasma concentrations [illegible] times, respectively, the therapeutic [illegible] concentrations in man (based on a 60 mg twice daily fexofenadine hydrochloride dose). No effect was observed on calcium channel current, delayed K^+ channel current, or action potential duration in guinea pig myocytes, Na^+ current in rat neonatal myocytes, or on the delayed rectifier K^+ channel cloned from human heart at concentrations up to 1 x 10^{-5} M of fexofenadine. This concentration was at least 32 times the therapeutic plasma concentration in man (based on a 60-mg twice daily fexofenadine hydrochloride dose).

Special Populations

In three, 2-week, multi-center, randomized, double-blind, placebo-controlled trials in patients 12-68 years of age with seasonal allergic rhinitis [illegible] fexofenadine hydrochloride 60 mg twice daily reduced total symptom scores [illegible] individual scores for sneezing, [illegible] itchy/watery/red eyes) compared to placebo. Statistically significant reductions in symptom scores were observed following the first 60-mg dose, with the effect maintained throughout the 12-hour interval. In general, there was no additional reduction in total symptom scores with higher doses [illegible] 0 mg twice daily. Although [illegible] some of the subgroups [illegible] significant differences in [illegible] fexofenadine hydrochloride across [illegible] defined by gender, age, and race. Onset of action for reduction in total symptom scores, excluding nasal congestion, was observed at 60 minutes compared to placebo following a single 60-mg fexofenadine hydrochloride dose administered to patients with seasonal allergic rhinitis who were exposed to ragweed pollen in an [illegible] associated with seasonal allergic rhinitis in adults and children 12 years of age and older. Symptoms treated effectively include sneezing, rhinorrhea, itchy nose/palate/throat, itchy/watery/red eyes.

CONTRAINDICATIONS

ALLEGRA is contraindicated in patients with [illegible] known hypersensitivity to any of its ingredients.

PRECAUTIONS

Drug Interactions

Fexofenadine has been shown to exhibit minimal [illegible] metabolism. However, co-administration [illegible] with ketoconazole and [illegible] led to increased plasma levels of [illegible]. Fexofenadine had no effect on the [illegible] of erythromycin and [illegible]. In two separate studies, fexofenadine HCl 120 mg BID (twice the recommended dose) was co-administered with erythromycin 500 mg every 8 hours or ketoconazole 400 mg once daily [illegible] conditions to normal, healthy [illegible], each study). No differences in adverse events or QTc interval were observed when subjects were administered fexofenadine HCl alone or in combination with erythromycin or ketoconazole.

The changes in plasma levels were [illegible] range of plasma levels achieved in adequate [illegible] well-controlled clinical trials.

The mechanism of these [illegible] been enhancing absorption, ketoconazole decreases fexofenadine gastrointestinal secretion, while erythromycin may also decrease biliary excretion.

Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential and reproductive toxicity of fexofenadine hydrochloride were assessed using terfenadine studies with adequate fexofenadine exposure (based on plasma area-under-the-curve [AUC] values). No evidence of carcinogenicity was observed when mice and rats were given daily oral doses of 50 and 150 mg/kg of terfenadine for 18 and 24 months, respectively; these doses resulted in plasma AUC values of fexofenadine that were up to four times the human therapeutic value (based on a 60-mg twice-daily fexofenadine hydrochloride dose).

In in-vitro (Bacterial Reverse Mutation, CHO/HGPRT Forward Mutation, and Rat Lymphocyte Chromosomal Aberration assays) and in-vivo (Mouse Bone Marrow Micronucleus assay) tests, fexofenadine hydrochloride revealed no evidence of mutagenicity.

In rat fertility studies, dose-related reductions in implants and increases in postimplantation losses were observed at oral doses equal to or greater than 150 mg/kg of terfenadine; these doses produced plasma AUC values of fexofenadine that were equal to or greater than three times the human therapeutic value (based on a 60-mg twice-daily fexofenadine hydrochloride dose).

Pregnancy

Teratogenic Effects: Category C. There was no evidence of teratogenicity in rats or rabbits at oral terfenadine doses up to 300 mg/kg; these doses produced fexofenadine plasma AUC values that were up to 4 and 37 times the human therapeutic value (based on a 60-mg twice-daily fexofenadine hydrochloride dose), respectively.

There are no adequate and well-controlled studies in pregnant women. Fexofenadine hydrochloride [illegible] pregnancy only if the [illegible] justifies the potential risk to the [illegible] effects. Dose-related decreases in pup weight gain and survival were observed in rats exposed to oral doses equal to and greater than 150 mg/kg of terfenadine; at these doses the plasma AUC values of fexofenadine were equal to or greater than 3 times the human therapeutic values (based on a 60-mg twice-daily fexofenadine hydrochloride dose).

Nursing Mothers

There are no adequate and well-controlled studies in women during lactation. Because many drugs are excreted in human milk, caution should be exercised when fexofenadine hydrochloride is administered to a nursing woman.

Pediatric Use

Safety and effectiveness of ALLEGRA in pediatric [illegible] up to two years of age [illegible] adverse events were similar in this group of patients [illegible] to patients above the age of 16 years.

Geriatric Use

In placebo-controlled trials, 42 patients, age 60 to 68 years, received doses of 20 mg to 240 mg of fexofenadine twice daily for up to two weeks. Adverse events were similar in this group to patients under age 60 years.

ADVERSE REACTIONS

In placebo-controlled clinical trials [illegible] 2461 patients receiving fexofenadine hydrochloride at doses of 20 mg to 240 mg twice daily, adverse events were similar in fexofenadine hydrochloride and placebo-treated patients. The incidence of adverse events, including drowsiness, was not dose related and was similar across subgroups defined by age, gender, and race. The percent of patients who withdrew prematurely because of adverse events was 2.2% with fexofenadine hydrochloride vs 3.3% with placebo. All adverse events that were reported by greater than 1% of patients who received the recommended daily dose of fexofenadine hydrochloride (60 mg twice-daily), and that were more [illegible] listed [illegible]

Adverse [illegible] fexofenadine hydrochloride (60 mg twice daily), but [illegible] were common in the placebo-treated group [illegible] headache and throat irritation.

The frequency [illegible] magnitude of laboratory abnormalities [illegible] were similar in fexofenadine hydrochloride [illegible] and placebo-treated patients.

OVERDOSAGE

Most reports of fexofenadine hydrochloride overdose contain limited information. However, dizziness, drowsiness, and dry mouth have been reported. Single doses of fexofenadine hydrochloride up to 800 mg (6 normal volunteers at this dose level), and doses up to 690 mg twice daily for one month (3 normal volunteers at this dose level), were administered without the development of clinically significant adverse events.

In the event of overdose, consider standard measures to remove any unabsorbed drug. Symptomatic and supportive treatment is recommended.

Hemodialysis did not effectively remove fexofenadine from blood (up to 1.7% removed) following terfenadine administration.

No deaths occurred at oral doses of fexofenadine hydrochloride up to 5000 mg/kg in mice (170 times the maximum recommended human daily oral dose based on mg/m^2) and up to 5000 mg/kg in rats (330 times the maximum recommended human daily oral dose based on mg/m^2). Additionally, no clinical signs of toxicity or gross pathological findings were observed. In dogs, no evidence of toxicity was observed at oral doses up to 2000 mg/kg (450 times the maximum recommended human daily oral dose based on mg/m^2).

DOSAGE AND ADMINISTRATION

The recommended dose of ALLEGRA is 60 mg [illegible] daily for adults and children 12 years of age [illegible]

[illegible] 60 mg once daily is recommended as the [illegible] use in patients with decreased renal [illegible] (See CLINICAL PHARMACOLOGY.)

HOW SUPPLIED

ALLEGRA 60-mg capsules are available in: high-density polyethylene bottles of 100 (NDC 0088-1102-47); HDPE bottles of 500 ([illegible]

ALLEGRA capsules have a white opaque cap and a pink opaque body with "1102" on the body or "allegra" on the cap and are supplied [illegible] at controlled room temperature 2[illegible]

[illegible] of June 1998A

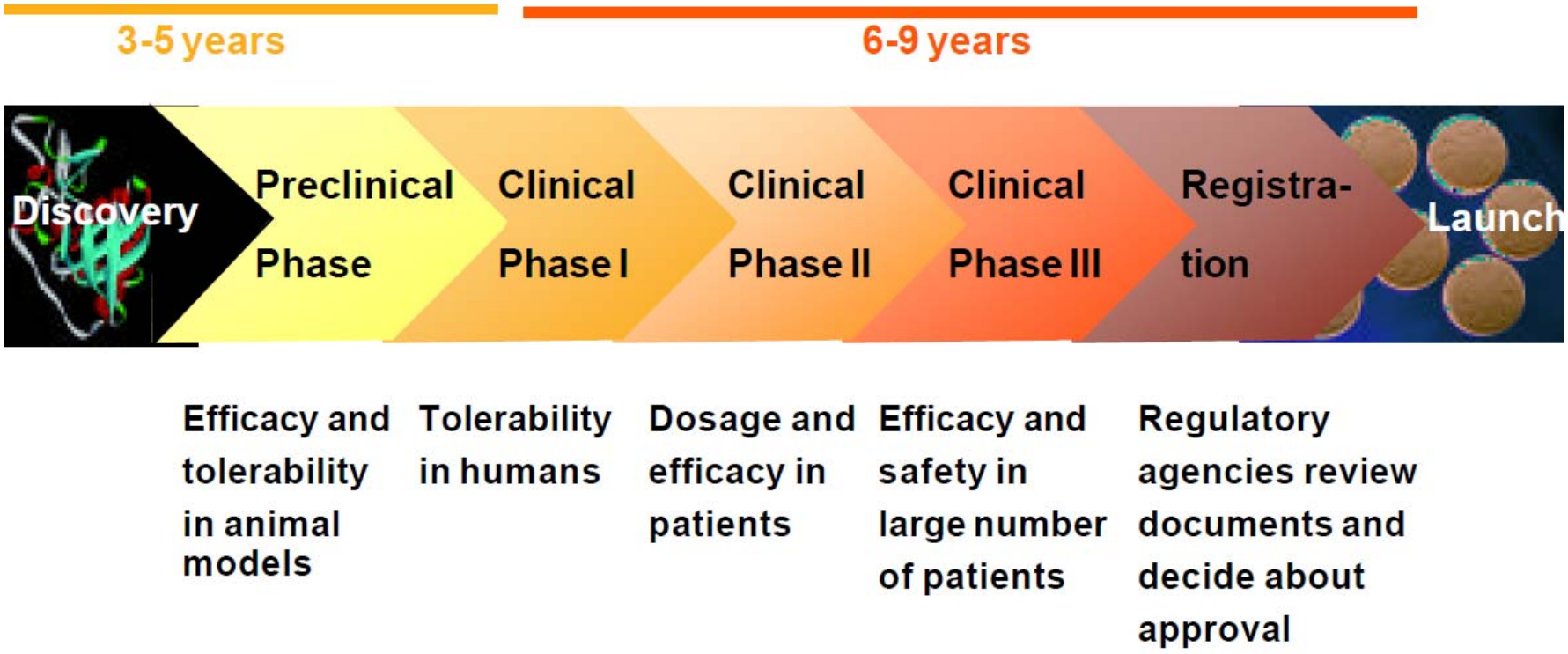
Hoechst Marion Roussel, Inc.
Kansas City, MO 64137 USA
US Patents 4,254,129; 5,375,693; 5,578,610.

Hoechst Marion Roussel

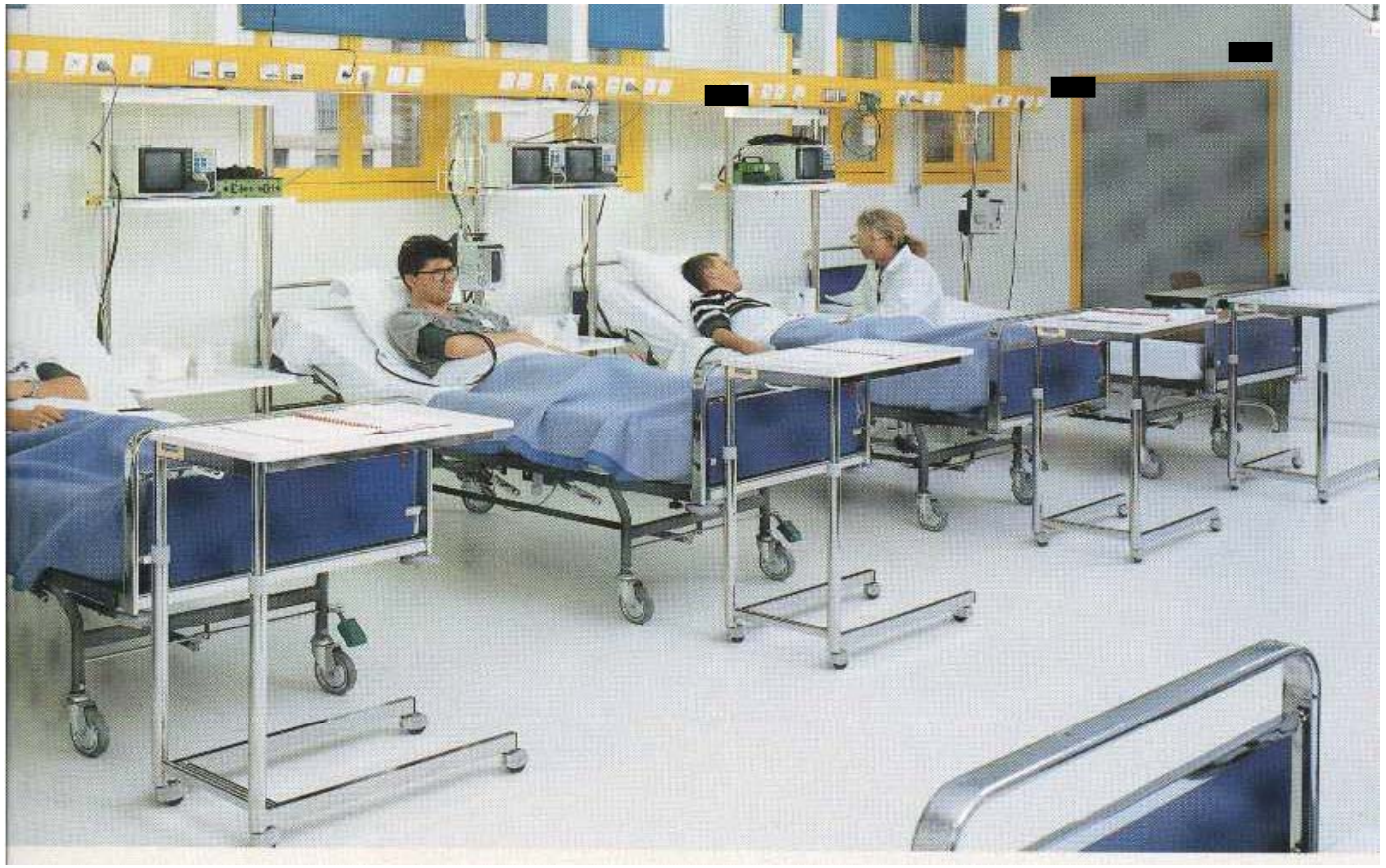
The Pharmaceuticals Company of Hoechst
Kansas City, MO 64134

Hoechst

Drug Development process



Phase 1 studies



Key Players
Roles and responsibilities

- Sponsor
  - may be an individual, company, institution or organisation
  - headquartered or represented in Switzerland
  - is responsible for the initiation, management and/or financing of a clinical trial
  - has the overall liability
  - may also be the investigator (sponsor – investigator)
  - is not necessarily the person financing the clinical trial (e.g. Investigator Initiated Trial – IIT)
  - may delegate any or/all of the trial-related tasks/duties and functions to an individual, company, institution or organisation (e.g. Contract Research Organisation – CRO)

Sponsor Clinical Trial Team

Drug Supply Study Manager

Drug Regulatory Affairs (DRA) Manager

Trial Data Manager

Biomarker Development

Clinical Trial Leader

Medical Writer

Translational Medicine Expert

Trial Statistician

Outsourcing Manager

Monitor(s)

Pharmacokineticist

Legal Counsel

Statistical Programmer

Database Developer

Bioanalyst

Key Players
Roles and responsibilities

- Investigator
  - responsible for the conduct of the clinical trial at a trial site
  - the welfare of the clinical trial subjects
  - the informed consent process
  - collection, documentation and archiving of data
  - reporting of adverse events to sponsor
- If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and usually called “principal investigator”

International Guidelines Governing Human Clinical Trials

- **Declaration of Helsinki**
  WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects- Brazil 2013 (new revised version)

- **ICH Guidelines**
  The tripartite harmonised ICH Guideline on Good Clinical Practice, ICH-GCP E6(R1), version dated 10 June 1996

- **Country/Region Specific Regulatory Guidances and Reviews (e.g. FDA, EMA)**

- **Ethical guidelines**
  CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subject (2002)

ICH = International Conference on Harmonization;
FDA = Food and Drug Administration; EMEA = European Medicines Agency

Good Clinical Practice (GCP)

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

Main Elements of ICH Guidelines for GCP

Institutional Review Board/
Independent Ethics Committee

Investigator

Informed Consent

Sponsor

Quality Assurance/Quality Control

Contract Research Organization (CRO)

Protocol Design

Clinical Protocol and Amendments

Investigator's Brochure (IB)

Essential Documents for Conduct of a Clinical Trial

Clinical Research in Switzerland

- Regulated by laws and ordinances (medicinal products and medical devices)
- Industry sponsored trials and Investigator Initiated Trials (IITs) are regulated in the same way
- Regulatory Authorities:

swissmedic
Swiss Agency for
Therapeutic Products

Schweizerische Eidgenossenschaft
Confédération suisse
Confederazione Svizzera
Confederaziun svizra

Eidgenössisches Departement des Innern EDI
Bundesamt für Gesundheit BAG

- Cantonal/Regional Ethics Committees:

swissethics
Schweizerische Ethikkommissionen für die Forschung am Menschen
Swiss Ethics Committees on research involving humans

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Applicable Swiss legislation

- Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (Therapeutic Products Act, TPA; SR 812.21)
  Bundesgesetz vom 15. Dezember 2000 über Arzneimittel und Medizinprodukte (Heilmittelgesetz, HMG; SR 812.21)
- Federal Act of 30 September 2011 on Research involving Human Beings (Human Research Act, HRA; SR810.30)
  Bundesgesetz über die Forschung am Menschen (Humanforschungsgesetz, HFG; SR810.30)
- Ordinance of 20 September 2013 on Clinical Trials in Human Research (Clinical Trials Ordinance; ClinO SR 810.305)
  Verordnung über klinische Versuche in der Humanforschung (Verordnung über klinische Versuche; KlinV; SR 810.305)
- Ordinance of 20 September 2013 on Human Research with the Exception of Clinical Trials (Human Research Ordinance, HRO; SR 810.301)
  Verordnung über die Humanforschung mit Ausnahme der klinischen Versuche (Humanforschungsverordnung, HFV SR 810.301)
- Organization ordinance on the HRA, org-HRA; SR 810.308
  Organisationsverordnung zum Humanforschungsgesetz (Organisationsverordnung HFG, OV-HFG; SR 810.308)
- Verordnung vom 2. Dezember 2011 über die Gebühren des Schweizerischen Heilmittelinstituts (Heilmittel-Gebührenverordnung, HGebV)

Approval

"Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks"
Section 2.2 ICH-GCP Guideline

Therefore prior approval by local Ethic Committee and relevant Regulatory Agency is required – to ensure the protection of patient rights, safety and well-beeing.

Required EC application documentation

- Study plan / protocol (and amendments)
- Case Report Form
- Patient Information sheet and informed consent form (in local languages)
- Compensation for participants
- Recruitment documentation
- Additional documentation for the participants (patient diary, questionnaires)
- Investigator‘s Brochure
- Investigator’s CV and proof of GCP training
- Details on infrastructure suitability and availability
- Details on the safe handling of personal data
- Contract

- **Proof of insurance**
  − or other proof of guarantee for any damage or injury, including the relevant agreements between the sponsor and the investigator

Liability

- *"Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured."*
  §15 Declaration of Helsinki

- *"If required by the applicable regulatory requirement(s), the sponsor should provide insurance or should indemnify (legal and financial coverage) the investigator/the institution against claims arising from the trial, except for claims that arise from malpractice and/or negligence.*
  The sponsor's policies and procedures should address the costs of treatment of trial subjects in the event of trial-related injuries in accordance with the applicable regulatory requirement(s)."
  Section 5.8 ICH-GCP Guideline

Liability

HFG Art. 19 Liability

- [1] Any person who carries out a research project involving persons shall be liable for damage suffered by them in connection with the project. The Federal Council may specify exemptions from liability.
- [2] Compensation claims become time-barred three years after the injured party has become aware of the damage and of the liable party, but no later than ten years after the completion of the research project. The Federal Council may specify a longer limitation period for particular research areas.
- [3] The provisions of the Code of Obligations[1] on tort are otherwise applicable; in the exercise of official duties, the Government Liability Act of 14 March 1958[2], or cantonal government liability law, is applicable. (1 SR 220, 2 SR 170.32)

Liability

- **KlinV §4, Art. 13 Requirements for liability coverage**

- [1] The liability coverage requirements can be fulfilled:

  a. by taking out insurance; or

  b. by providing security of equivalent value.

- [2] The policy value shall be set in accordance with Annex 2.

- [3] The liability coverage must cover damage occurring up to ten years after the completion of the clinical trial.

Indemnity

A written guarantee inserted in the protocol, contract or subject information leaflet, that the sponsor will compensate a trial subject who is harmed by taking part in a clinical trial.

- Before the start of a commercially sponsored trial, the sponsor must indemnify the investigator against any loss incurred by the investigator (including the cost of legal representation) as a result of claims arising from the trial, except to the extent that such claims arise from the negligence of the investigator for which the investigator remains responsible.
- Purpose is to ensure that in the event of injury there is a facility that compensation (financial) can be paid to reinstate the claimant to the same financial position that they were in prior to the incident.

Insurance

Contract or policy that provides cover for the sponsor or investigator in the event of a claim for damages by a trial subject.

- In relation to the sponsor's obligation to comply with the above compensation policy, the sponsor must ensure that insurance or indemnity is in place to cover its liability and that of the investigator.
- Typically a multi-national clinical trials program will consist of a combination of global master policy plus individual local policies on a per trial/per country basis.
- The Institution / clinical trial unit must have appropriate and adequate indemnity insurance to cover claims or damages for negligence, for which it shall be liable.
- Also, physicians involved with the trial should have insurance – such as that offered by a medical defence organization – that will respond to any negligence claim. Nurses should hold professional indemnity insurance.

Insurance

- **HFG Art. 20 Coverage**

- [1] Liability must be appropriately covered through insurance or in some other manner. The Federal Government and its public-law institutions and corporations are exempt from the liability coverage requirements.

- [2] The Federal Council may:

  a. specify requirements for insurance and other forms of coverage;

  b. exempt research areas or classes of damage from the liability coverage requirements.

- [3] For the protection of the injured party, it may:

  a. grant this party a direct claim against the party providing liability coverage;

  b. restrict the cancellation rights and objections of the party providing liability coverage, while granting appropriate rights of recourse.

Insurance

- **KlinV Annex 2 (Art. 13) Policy values for liability coverage**
- 1. For Category A clinical trials where any measures for the collection of health-related personal data or the sampling of biological material entail more than only minimal risks and burdens, the policy value shall be at least:

  a. per person: 250 000 Swiss francs;

  b for damage to property: 20 000 Swiss francs;

  c. for the entire clinical trial: 3 million Swiss francs.

- 2. For other clinical trials, the policy value shall be at least:

  a. per person: 1 million Swiss francs;

  b. for damage to property: 50 000 Swiss francs;

  c. for the entire clinical trial: 10 million Swiss francs.

Indemnity and insurance: ICF

- It must be ensured that the language in the local ICF is fully congruent with any contract between the investigator, institution, sponsor, and any further applicable partner.
- The ICF may not include exculpatory language which releases or appears to release the investigator, the sponsor, the institution, or their legal agents from liability for negligence (ICH 4.8.4).
- The subject's existing legal rights must be protected. The compensation and/or treatment available to the subject in the event of trial-related injury must be stated.
- The ICF should explain how to make a claim and where to seek further information.

Q&A

Back-up slides

Development – Phases

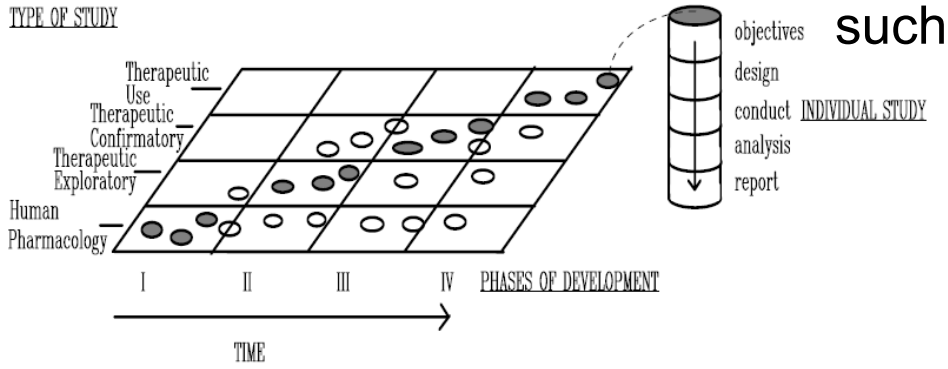
Pre-Clinical Phase →	Research that begins before clinical trials (testing in humans); laboratory testing/animal studies
Proof-of-Concept (PoC) →	Studies which allow a preclinical hypothesis about mechanism of action to be tested and demonstration of potential therapeutic benefit to patients
Phase I (Human Pharmacology) →	Clinical trials in humans (20-80 patients or healthy volunteers) to estimate initial safety and tolerability
Phase II (Therapeutic Exploratory) →	Clinical trials in humans (100-300 patients) of which the primary objective is to explore therapeutic efficacy in patients

Development - Phases

Phase III
(Therapeutic Confirmatory) → Clinical trials in humans (1000-3000 patients) of which the primary objective is to demonstrate or confirm therapeutic benefit

Phase IV
(Therapeutic Use) → Clinical trials in humans (large numbers) performed after marketing authorisation to go beyond the prior demonstration of drug safety, efficacy and dose definition (other than routine surveillance or non-interventional studies such as PMS)

Correlation between Development Phases and Types of Study



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Declaration of Helsinki

WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

http://www.wma.net/en/30publications/10policies/b3/index.html

International Conference on Harmonization (ICH)
of Technical Requirements for Registration of Pharmaceuticals for Human Use

- **"Quality" Topics**, i.e., those relating to chemical and pharmaceutical Quality Assurance (Stability Testing, Impurity Testing, etc.)
- **"Safety" Topics**, i.e., those relating to in vitro and in vivo pre-clinical studies (Carcinogenicity Testing, Genotoxicity Testing, etc.)
- ***"*Efficacy" Topics**, i.e., those relating to clinical studies in human subject (Dose Response Studies, Good Clinical Practices, etc.)
- **"Multidisciplinary" Topics**, i.e., cross-cutting Topics which do not fit uniquely into one of the above categories (MedDRA, ESTRI, M3, CTD, M5)

ICH home page: ***http://www.ich.org/products/guidelines.html***

International Conference on Harmonization (ICH) Guidelines for Efficacy

Finalised Guidelines (*Step 4*)

E1	The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions	Oct. 1994
E2A	Clinical Safety Data Management: Definitions and Standards for Expedited Reporting	Oct. 1994
E2B(R2)	*Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports* (This guideline is re-opened for revision under *Step 2*. See E2B(R3)).	Feb. 2001
E2C(R1)	Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs *(The Addendum dated February 2003 has been incorporated into the core guideline in November 2005).*	Nov. 1996
E2D	Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting	Nov. 2003
E2E	Pharmacovigilance Planning	Nov. 2004
E3	Structure and Content of Clinical Study Reports	Nov. 1995
E4	Dose-Response Information to Support Drug Registration	March 1994
E5(R1)	Ethnic Factors in the Acceptability of Foreign Clinical Data	March 1998
E6(R1)	Good Clinical Practice: Consolidated Guideline	May 1996
E7	Studies in Support of Special Populations: Geriatrics	June 1993
E8	General Considerations for Clinical Trials	July 1997
E9	Statistical Principles for Clinical Trials	Feb. 1998
E10	Choice of Control Group and Related Issues in Clinical Trials	July 2000
E11	Clinical Investigation of Medicinal Products in the Pediatric Population	July 2000
E14	The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs	May 2005
E15	Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories	Nov. 2007