Introduction to
Clinical Trials

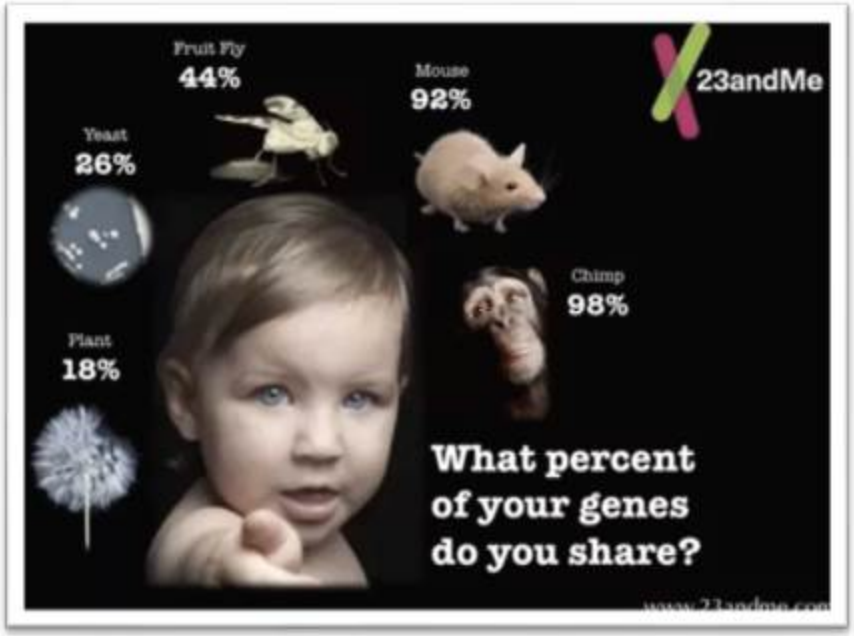
Module 3 Topic 1

Clinical Trials

- Laboratory rats share around 98% DNA with humans
- Animal studies give us important details about a new drug's safety and efficacy.
- Results of animal studies may give us a lead to human effects, but cannot be relied on totally.
- They are no alternative to human studies.

Genetic Similarity

Figures vary between different publications, however the absolute number is not very important. What is important is that we are quite similar to laboratory animals.



Laboratory animals

In laboratories, we use inbred strains. A strain is inbred when it has undergone at least 20 generations of brother x sister mating. Such animals are isogenic (genetically identical). Their response to an intervention is more or less identical.

Final Test

The final test of a drug meant for human beings is on humans. But we humans are quite heterogenous in so far as genetics is concerned, since we are not in-bred as laboratory animals are. Each of us responds slightly differently to interventions.

Predictive value

- Predictive value of animal studies is good, in so far as safety is concerned.
- Animal studies are poor predictors or efficacy in the humans, for reasons such as:
  - Changes in mood, sleep cycle etc., are difficult to measure in animals
  - Many drugs do not have any effect on healthy animals, hence the need for animal models of disease.
  - Many animal models are available for study of drugs, but most of them do not mimic the human disease.

Human Trials

- Human studies begin with reassessing safety in humans in Phase I
- These studies are conducted on repeat dose and escalating dose levels.
- Following this, efficacy is studied in patients with the disease, for which the drug is indicated. The dose range and schedule are finalized in this study.
- Lastly studies are conducted on large number of patients, these are similar to those encountered in clinics and hospitals.
- Special studies (in children, old people or people with some dysfunction) may be carried out.

Phase 0

(Introduced by FDA following Phase I accidents like TGN 1412)

Objective: To study the biological handling of the drug by the human being.

Participants: Small number (6 to 10) healthy individuals, male, are exposed to a very small amount of the drug (<100 mcg). The movement of the dug in the body is traced. Often radiolabeled drug is used.

Site: Specialized centers, often study done in ICU, with well experienced investigators, supported by sophisticated bioanalytical units.

End points: Level of drug in body fluids and tissues is traced.

Phase I

Objective: To study the safety and pharmacokinetics of the drug. If possible the efficacy is measured.

Participants: Small number (20 to 80) of healthy individuals, gender depends upon the nature of the drug.

Study design: Usually no controls, blinding etc. is used. Doses may be repeated and/or escalated depending on the intended use of the drug.

Site: Specialized centres, often study done in ICU, with well experienced investigators.

End points: Every physiological and biochemical variable that can be measured is measured.

Phase II

Objective: To explore the efficacy of the drug in patients suffering from disease that the drug is intended for, and to decide the dose and schedule for Phase III studies.

Participants: Moderate number (up to 200) of patients, a homogenous group with as few co morbidities, gender depends upon the nature of the drug.

Study design: Usually no controls, blinding etc. is used. Various doses and schedules of the drug may be studied.

Site: Specialized centres, usually in hospitals, with experienced investigators.

End points: Changes are measured in parameters related to efficacy and safety of the drug.

Phase III

Objective: To confirm the efficacy of the drug in patients, and comparing it with the available standard treatment. Patients with comorbidities allowed, within reasonable limits.

Participants: Large number (up to 5000) of patients, of either gender (unless the drug has gender related effects).

Study design: Multicentre, double blind, standard controlled, randomized studies are most favoured

Phase III

Site: Could be hospital based or even OPD based, investigators with clinical research experience are preferred.

End points: Parameters are chosen to reveal efficacy and safety of the drug.

Randomization

- A method based on chance alone by which study participants are assigned to a treatment group. **Randomization** minimizes the differences among groups by equally distributing people with particular characteristics among all the trial arms.

Types of Randomization

- Simple Randomization is based on a single sequence of random assignments is known as simple randomization.
- Block Randomization is designed to randomize subjects into groups that result in equal sample sizes.
- Stratified Randomization addresses the need to control and balance the influence of covariates.
- Covariate Adaptive Randomization, assigns a new participant to a particular treatment group by taking into account the specific covariates and previous assignments of participants.

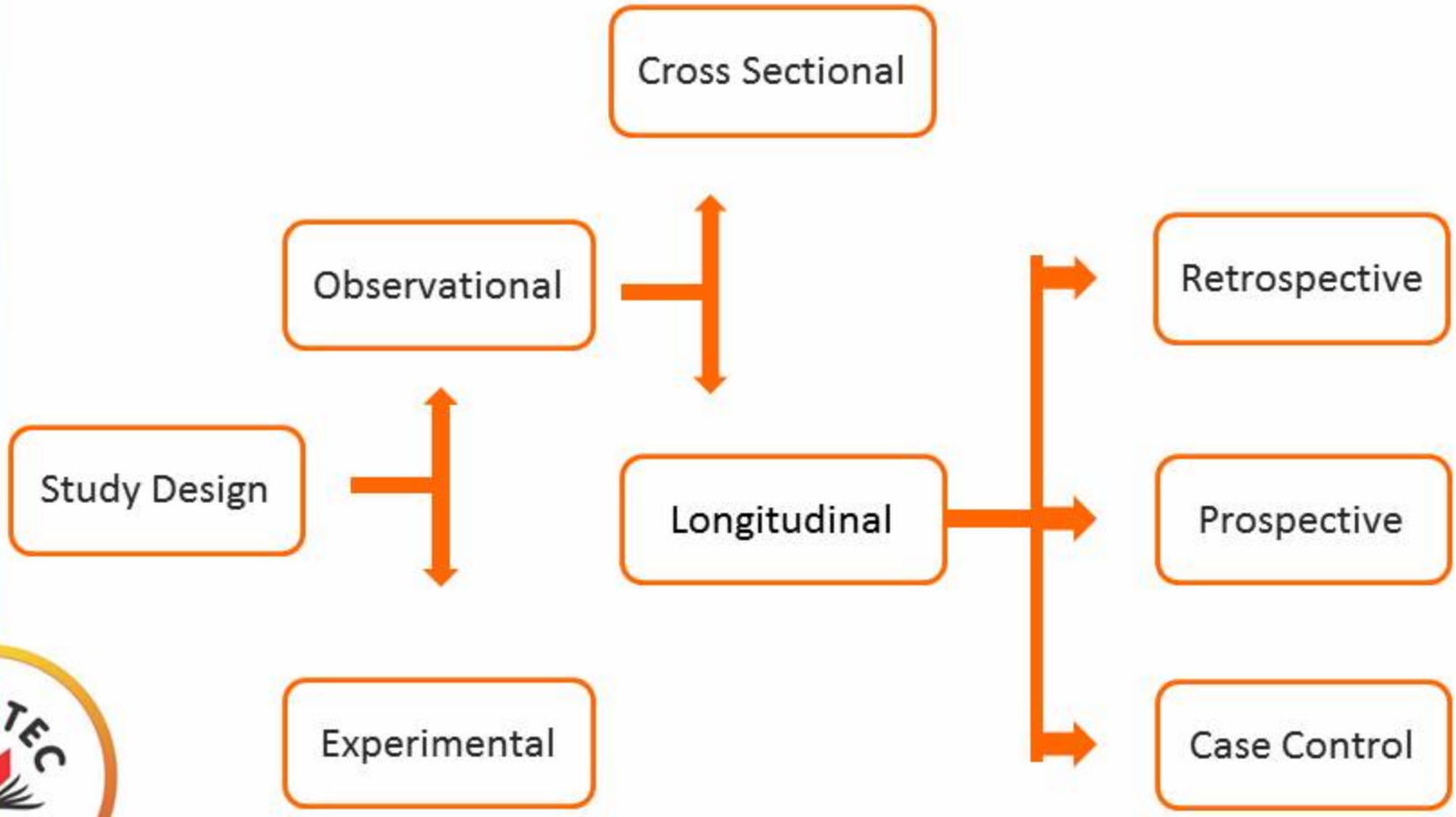
Blinding

- A method in which the participants, the investigators or those who analyses results do not know the treatment given to participants.
- In single blind studies, only the participants do not know what they are receiving.
- In double blind studies, both the participants and investigators do not know the identity of medication given to participants
- In triple blind studies, the participants, investigators and data analysts do not know the identity of treatments given to participants.

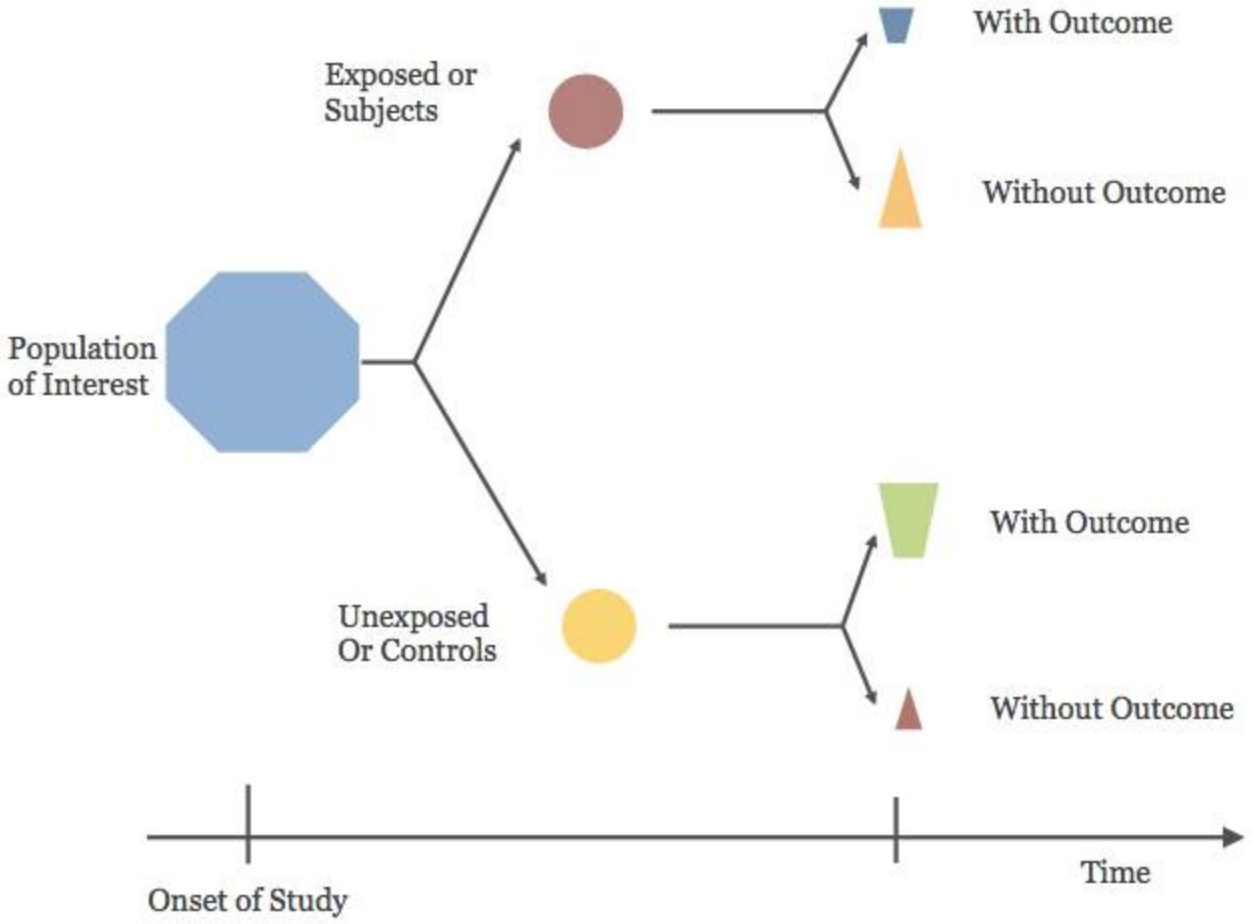
Sample size

- All trials are done on a sample of participants, and not the entire population of those who suffer from the disease.
- The sample drawn from the universe must represent the universe and should be adequate to draw an inference about the entire population.
- Statisticians calculate the sample size, using the following values:
  - Total size of the universe
  - Margin of error
  - Confidence interval
  - Standard deviation of the data

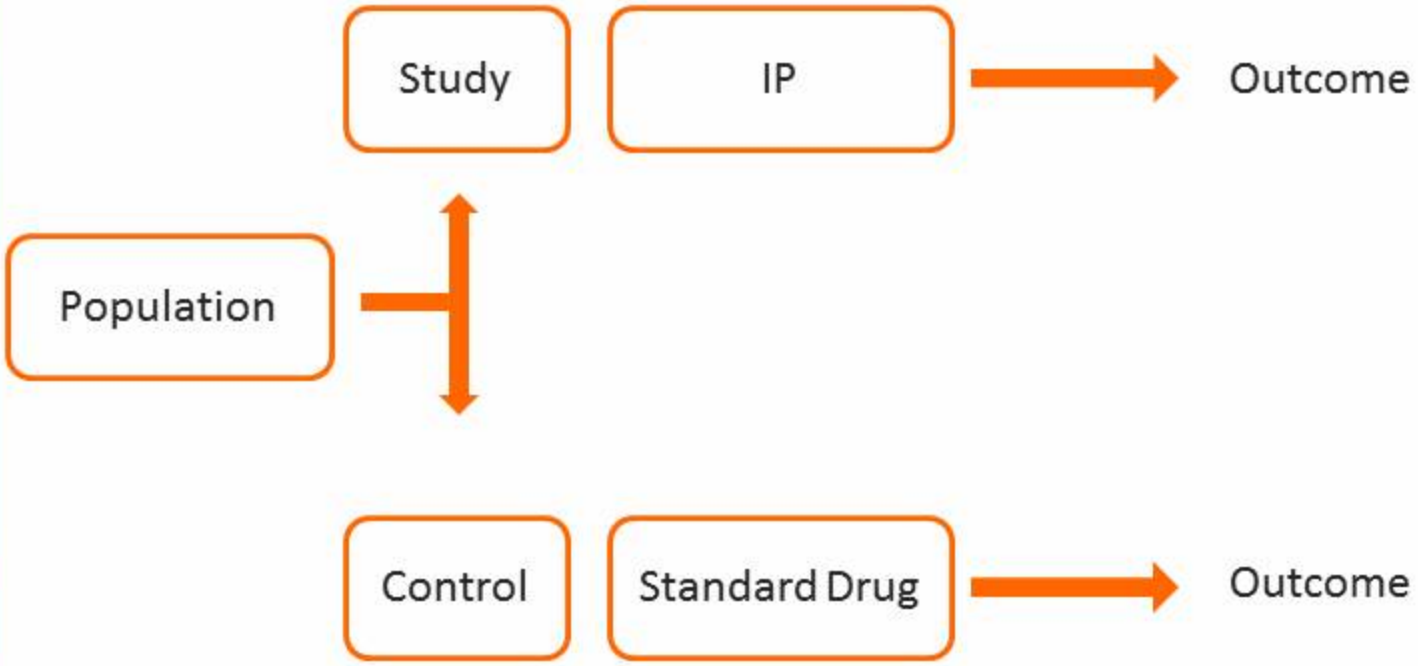
Clinical Trial Designs



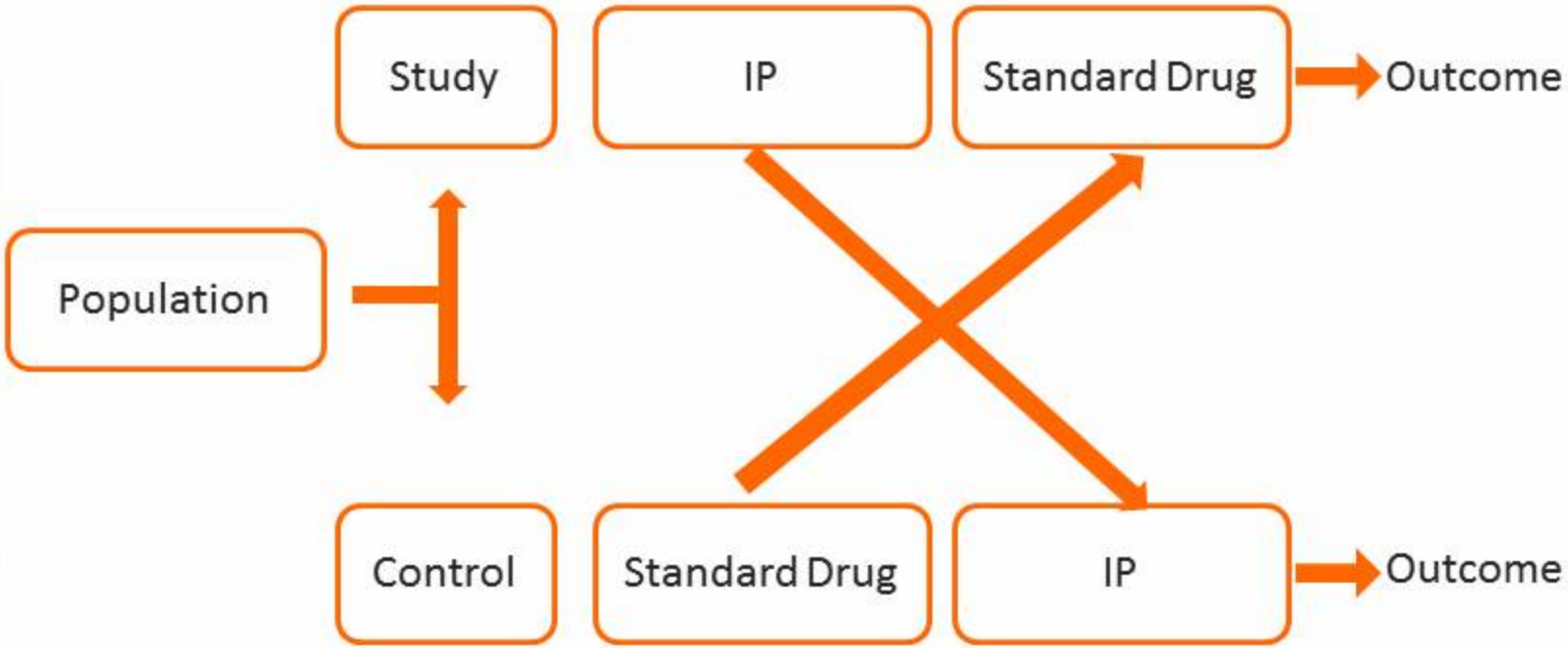
Randomized Controlled Trial



Parallel Design



Crossover Design



Adaptive Design

- Adaptive designs have been around since 1970s, but have gained importance due to falling research output.
- This design allows modifications to the trial and/or statistical procedures of the trial after its initiation without undermining its validity and integrity.
- In these studies the method of randomization, sample size, biomarkers, and even the hypotheses may be changed on interim analysis.
- The interim analysis has to be included in the original design and data obtained before and after the analysis can be included in the final analysis.

Control Groups

- The inclusion of an individual in a trial produces effects, not all of which are attributable to the study drug. Comparison of the effects with those produced in another individual not receiving the drug is necessary. This is the basis of controls.
- In the past placebos were used as controls, but considering the risk of use of placebos, they are now replaced with known standard therapies. Placebos may still be used if there is no treatment available for the disease under study.

Types of Controls

- Placebo concurrent control
- No-treatment concurrent control
- Dose-response concurrent control
- Active (positive) concurrent control
- External control (including historical control)
- Multiple control groups

Study Schedules

Most studies include a recruitment phase a treatment and a follow-up phase. There could be additionally a run in or a wash out phase.

Informed Consent

- Ethics dictates that every participant is recruited only after he/she has given an informed consent.
- The prospective subject should be explained all risks and benefits of the trial, in a language understood by the participant.
- In case the participant is unable to take a decision (legal or medical incompetence) a legally authorized representative may do so.

Informed Consent (contd)

- In case the participant is unable to record the decision, the process should be conducted before a witness.

- In India, when vulnerable subjects are involved, and the study is on a new drug, AV recording is mandatory.

General Principles

- Control groups and treatment groups should be similar to start with, this is usually achieved by random allocation.
- If the groups are grossly unequal, then it is difficult to answer the research question.

General Principles

- Design, end points, sample size, statistical plan must be decided before beginning the study, and detailed in the protocol. No deviation from the protocol is allowed.
- One cannot change the goal posts in the middle of the game.

General Principles

- Minor deviations from the protocol are inevitable, when they are expected, waivers should be obtained.
- If unplanned deviations take place, the cause should be identified, and corrective and preventive actions (CAPA) initiated.
- Impact and incidence of deviations is inversely proportional

Incidence

Impact

Adverse Events

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

ICH GCP E6 R2

Adverse Drug Reactions

In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established: all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase responses to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

ICH GCP E6 R2

Serious Adverse Event

- Any untoward medical occurrence that at any dose:
  - results in death,
  - is life-threatening,
  - requires inpatient hospitalization or prolongation of existing hospitalization,
  - results in persistent or significant disability/incapacity,

    or
  - is a congenital anomaly/birth defect

Data Collection

- All trial data is collected in the CRF and transmitted to the sponsor/data management center.
- Newer systems of data collection allow direct entry of data into a software, this eliminates entries on paper and transfer to the software.
- Data management does the data entry and cleaning, raises queries and when all data is collated, locks the database for statistical analysis.
- On completion of data analysis the sponsor is in a position to prepare the Clinical Study Report.

Archiving

- Archiving is the responsibility of the sponsor, but may be outsourced to archiving agencies.
- All essential documents of clinical trials should be archived and preserved for a period specified in the relevant rules.
- Essential study documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.
- Since it is uncertain when the last application will be made, storage is required for an indefinite period.