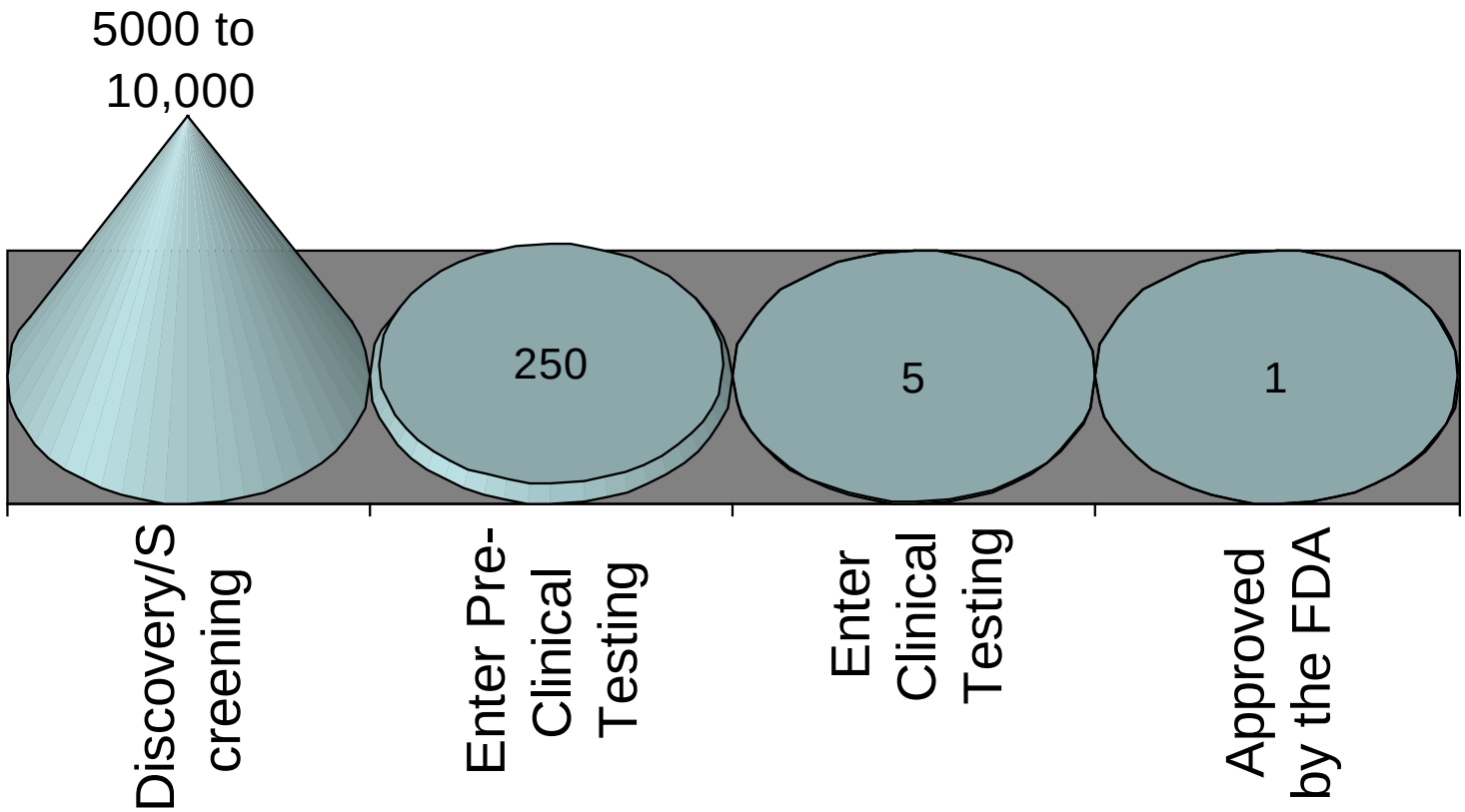
30th PREMA ANNIVERSARY

Introduction to Drug Development Process

Objectives

- **Recognize the investigational drug success rates by stages**
- **Define pre-clinical studies**
- **Define Investigational New Drug Application**
  - Phase I, II, III Studies
- **Define New Drug Application**
- **Define phase IV studies**

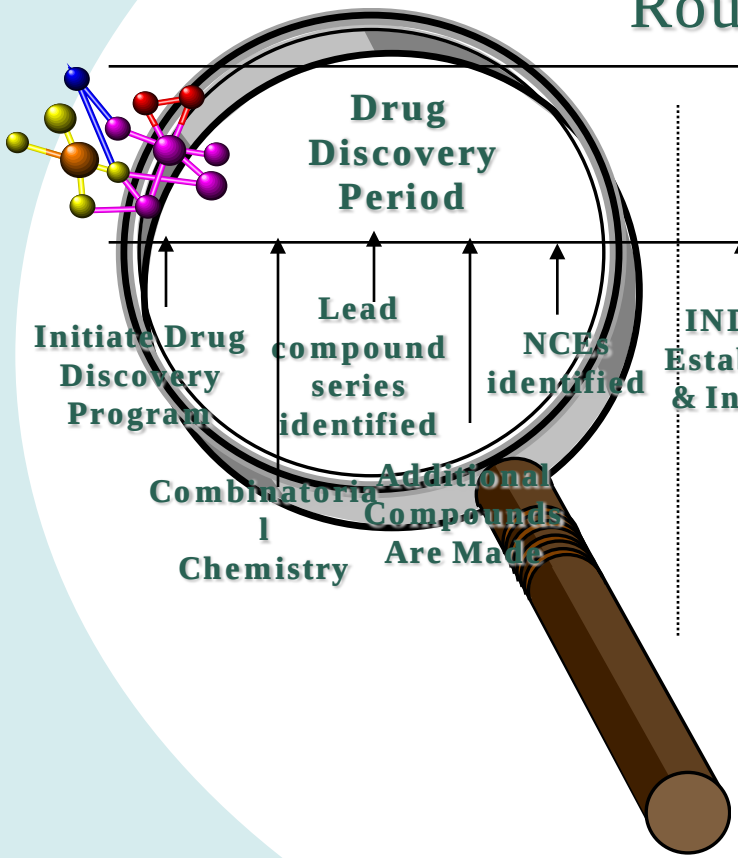
Investigational Drug Success Rates by Stage



Source: PhRMA, Tufts Center for the Study of Drug Development

4- 10 YEARS

Roughly $1.7 Billion



Drug Discovery Period

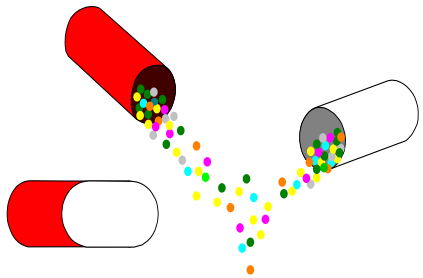
- Initiate Drug Discovery Program
- Combinatorial Chemistry
- Lead compound series identified
- Additional Compounds Are Made
- NCEs identified

Drug Development and Registration Period

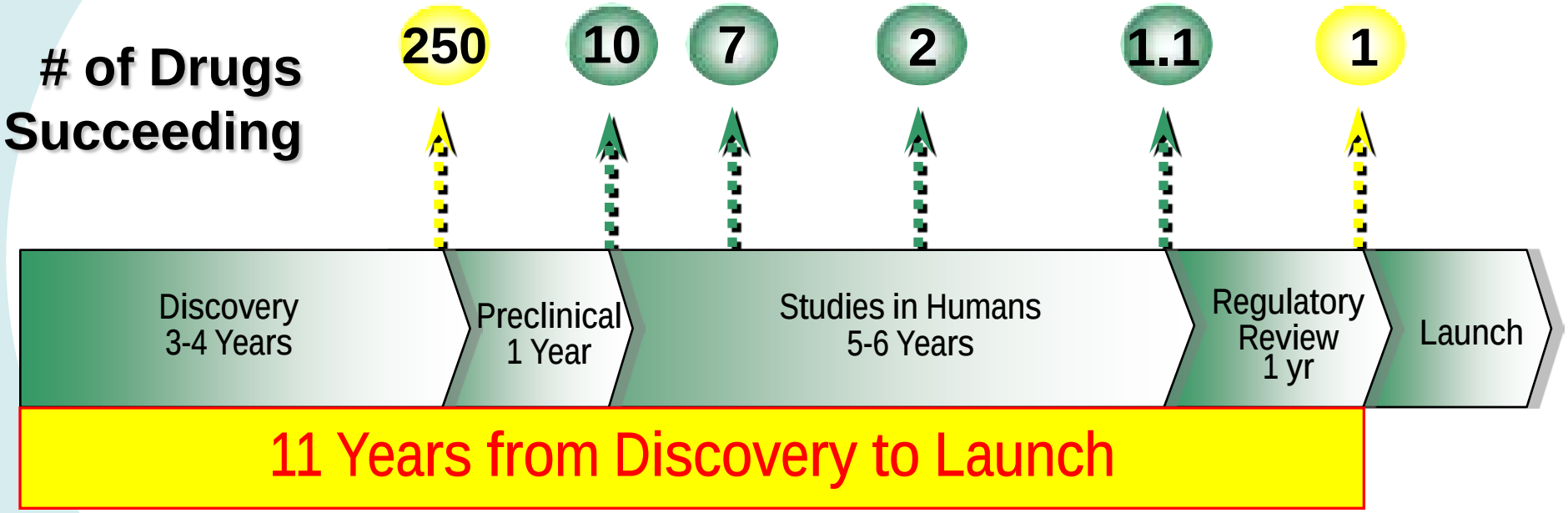
- IND Plan Established & Initiated
- IND Filed
- Clinical Studies Initiated
- NDA Prepared & Submitted
- NDA Approved
- Dug Launched

Drug Marketing & Line Expansion

- Post-Marketing Surveillance Initiated
- New Clinical Indications Pursued
- New Dosage Forms & Formulations Developed
- Activities Conducted to Support Marketing



How We Discover & Develop New Drugs



Source: PhRMA

Pre-Clinical Studies

- Single Dose Toxicity Studies
- Repeated Dose Studies
- Safety Pharmacology Studies
- Genotoxicity Studies
- Carcinogenicity Studies
- Reproductive Toxicity Studies
- Data Collected in Animal Studies

Investigational New Drug Application

The product of successful Preclinical development

If the investigational New Drug submission is accepted, the compound begins Phase I –IV clinical trials. Long-term preclinical trials continue.

Trial Design

- **Normal, usually healthy, volunteer subjects**
- **Few subjects (20-100)**
- **Typically single center**
- **Usually no benefit to subjects**

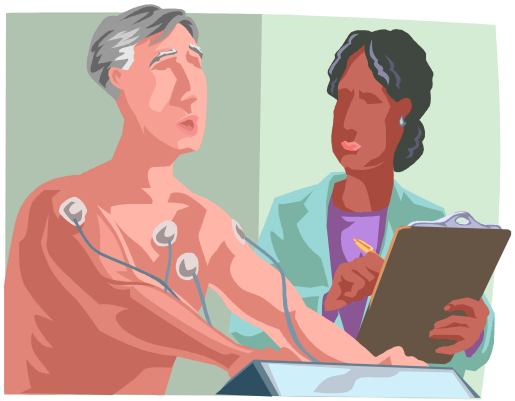
- **Duration: *Short* – from days to several weeks or months**
- **Open label – *no placebo or comparative agent***
- **Uncontrolled**
- **Single or multiple doses**

Purpose\Objective

- **Mechanism of action (ADME) and PK/PD**
- **Pharmacological effect**
- **Tolerability, side effects, and toxicity as dose escalates**
- **Early evidence of efficacy**
- **Evaluates Safety *only***
  - Identify the most likely potential toxicities (Adverse Events or Serious Adverse Events)
  - Identify most likely dose range (Distribution)

Trial Design

- **Patients with the targeted disease or condition**
- ***Several hundred (100-300)***
- **Duration – several months to 2 years**
- **Randomized**
- **Placebo or active control**
- **Parallel, double-blind**
- **Single or multiple doses**
- **Multicenter**



Purpose\Objective

- Dose range finding (minimum/maximum effective dose)
- Effectiveness (small scale) for treatment of the disease or condition for which the drug is intended
- Maximum Tolerated Dose (MTD)
- Common short-term side effects and risks in individuals whose health is impaired.
- Pharmacokinetics

Seeks to answer :

- the drug's efficacy in patients
- short-term adverse effects in patients
- theoretical advantage over other therapies
- what is a well-tolerated, effective dose range

Clinical Research
Phase III (Therapeutic confirmatory): Pivotal trials

Trial Design

- **Patients with the targeted disease/condition**
- **Approximates "real life"**
  - *"looser" inclusion/exclusion*
- **Several 1,000 – 3,000 patients**
  - *Gender should mirror the population*
- **Duration – 1 to 4 years**
- **Randomized**
- **Placebo or active control**
- **Parallel, double-blind**
- **Multicenter**

Phase III (Therapeutic confirmatory): Pivotal trials

Purpose\Objective

- **Effectiveness (large scale)**
- **Relative risk/benefit relationship**
- **Long term safety information including**:
  - common side effects
  - drug interactions
  - age/race/gender differences
- **Long term side effects (for labeling)**
- **Dosing (for labeling)**
- **Careful assessment of safety and efficacy**
  - Direct support of marketing claims

New Drug Application

- **The vehicle in the USA through which sponsor formally propose that FDA approve a new drug**
- **Clinical data is only a small component of the NDA**
- **Do benefits outweigh the risks?**
- **Is labeling accurate?**
- **Are manufacturing methods adequate?**

Application to Market New Drug in the US

New Drug Application (NDA) :

- **up to 800 Volumes**
- **350 pages per Volume**

Therefore :

- **280,000 pages**
- **laid end to end 78 Km of paper**

HAS TO BE DONE IN DUPLICATE !!!

Putting together an NDA/MAA !!

Launch

After receiving approval from the regulatory agency (ies) the drug can be “launched” into the marketplace.

Commercialization

Phase IV: Post-Marketing

Therapeutic use

Phase IV: Post-marketing

Trial Design

- Several hundred to several thousand subjects with the disease or condition
- Reflect conditions of ordinary medical practice
- Randomized
- Placebo or active control
- Multi-center

Phase IV: Post-marketing

Purpose\Objective

- **Perform Quality of Life (QOL) trials**
- **Perform pharmacoeconomic trials**
  - Is the drug more cost effective than other treatments?
- **Collect long term safety information**
  - Epidemiology studies for safety (may be a condition for approval)
  - Additional surveillance for unexpected or rare adverse events
- **Add line extensions**
  - New formulations – how can we use this drug in the future?

Questions and Answers

Good Clinical Practices Overview

Objectives

- Understand historical events
- Identify the purpose of ICH-GCP
- Understand fundamental Principles of ICH-GCP
- Discuss ICH-GCP guidelines
- Describe roles and responsibilities of various stakeholders in clinical trials
- Differentiate key documents in clinical research
- Recognize benefits of GCP

Good Clinical Practice?

Study 1:

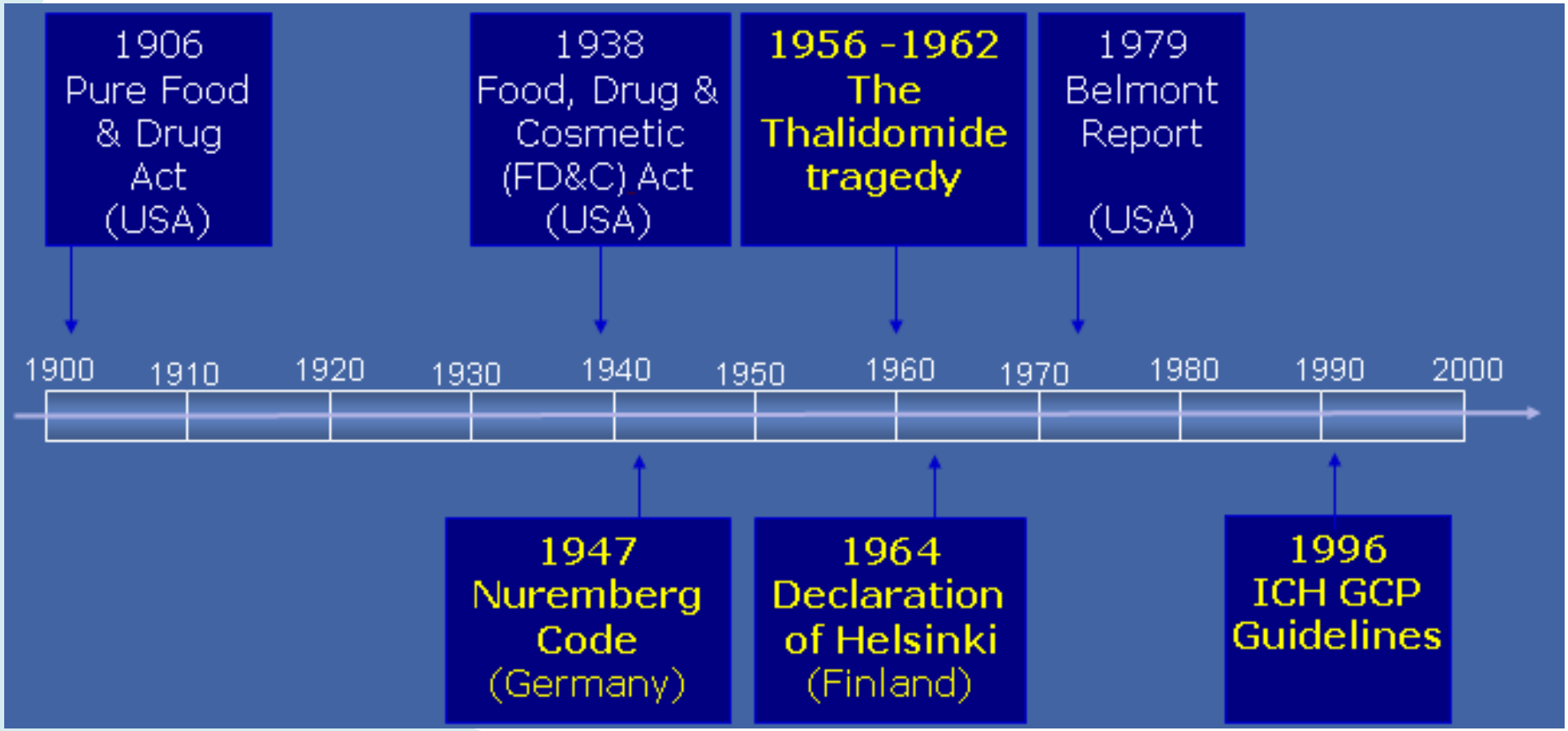
To learn how to warm hypothermic patients, study subjects were first submersed in freezing water for 3 hours.

Study 2:

To advance transplant medicine, legs of subjects were amputated and attached to another.

- **Study 3:**
- **To study the natural history of syphilis, antibiotics were witheld from prisoners with early syphilis.**

Historical milestones:



What is ICH?

"International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use"

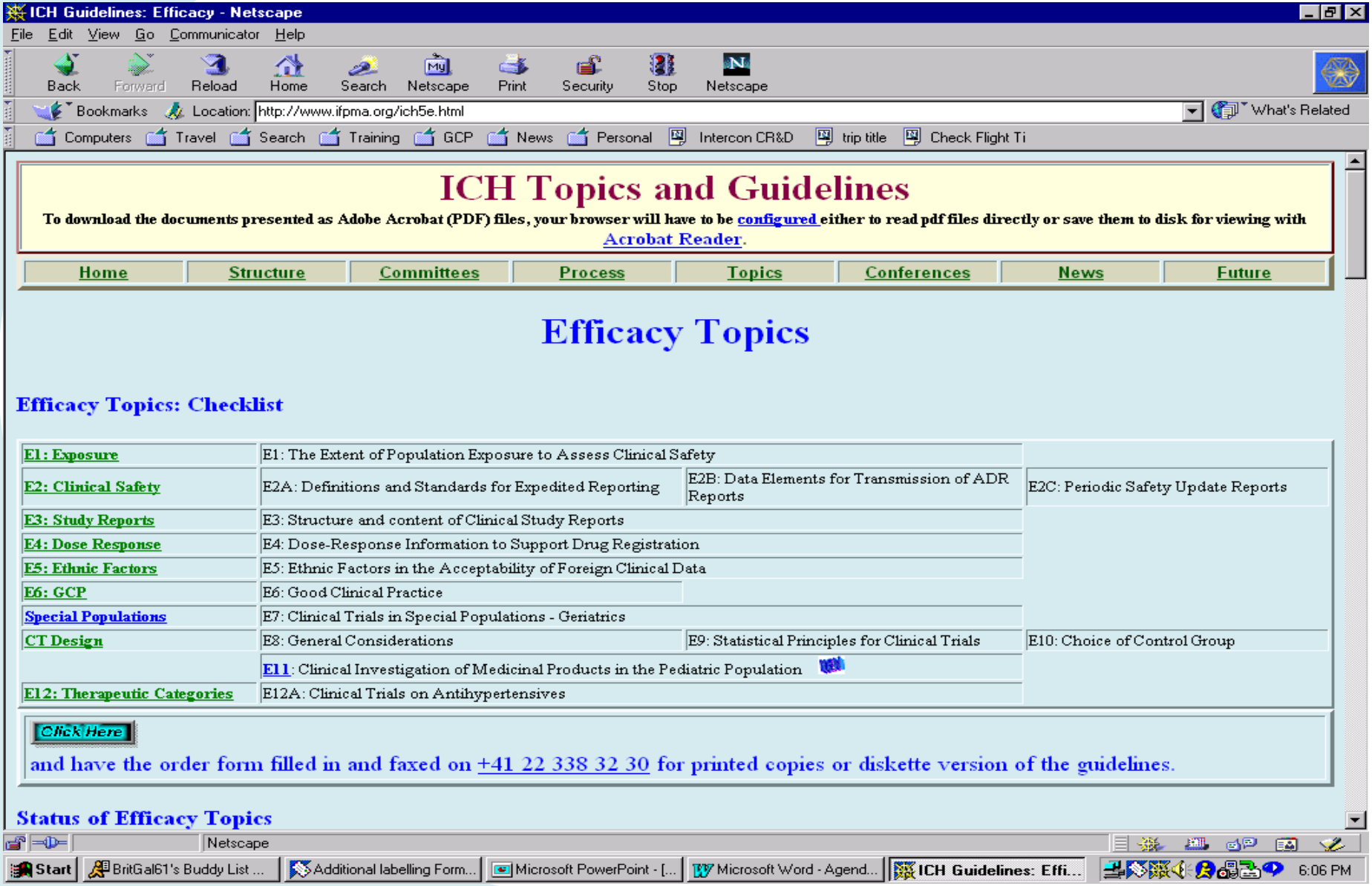
- **Brings together:**
  - **Regulatory Authorities**
  - **Experts from the pharmaceutical industry**
- **To:**
  - **Discuss scientific and technical aspects of drug registration**
- **Aims:**
  - **Economical use of resources**
  - **Expedite approval of new drugs while maintaining quality, safety, efficacy and regulatory obligations**

What is ICH-GCP?

ICH provides 4 categories of guidelines:

- **Quality**
- **Safety**
- **Efficacy**
- **Multidisciplinary**

http://www.ifpma.org/ich6e.html



Guidelines >>

Q S E M

Find quickly What's new on the ICH site

UMC and MedDRA MB Announce MedDRA's implementation in Vigibase March 18, 2008

Read here the Tokyo Symposium Proceedings: Hot Topics and Influence on Asia

General
E14 related
GCG related
MedDRA related

Clinical Safety

E1	*The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life Threatening Conditions*	*E1*
E2A	*Clinical Safety Data Management: Definitions and Standards for Expedited Reporting*	*E2A*
E2B(R3)	*Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports*	*E2B(M)*
E2C(R1)	*Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs*	*E2C*
	Addendum to E2C: Periodic Safety Update Reports for Marketed Drugs **(in E2C(R1))**	*E2CA*
E2D	*Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting*	*E2D*
E2E	*Pharmacovigilance Planning*	*E2E*

Clinical Study Reports

E3	*Structure and Content of Clinical Study Reports*	*E3*

Dose-Response Studies

E4	*Dose-Response Information to Support Drug Registration*	*E4*

Ethnic Factors

E5(R1)	*Ethnic Factors in the Acceptability of Foreign Clinical Data*	*E5*

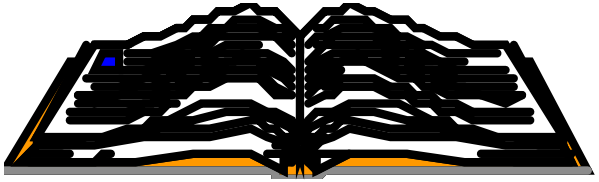
Good Clinical Practice

E6(R1)	*Good Clinical Practice*	*E6*

Clinical Trials

ICH

"Good Clinical Practices: Consolidated Guideline" finalised May 1996



Developed with consideration

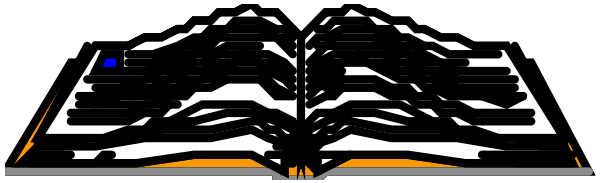
of the current GCPs of:

European Union	Japan	United States
Australia	Canada	Nordic Countries
World Health Organization (WHO)		

ICH Guideline for GCP

Contents

1. Glossary
2. The Principles of ICH-GCP
3. IRB / IEC
4. Investigator
5. Sponsor
6. Protocol and Amendments
7. Investigator's Brochure
8. Essential Documents for the Conduct of a Clinical Trial



13 Principles of GCP

1. Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).

2. 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.

3. The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.

4. The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.

5. Clinical trials should be scientifically sound, and described in a clear, detailed protocol.

13 Principles of GCP

6. A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favourable opinion.

7. The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.

8. Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).

9. Freely given informed consent should be obtained from every subject prior to clinical trial participation.

10. All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.

13 Principles of GCP

11. The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

12. Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.

13. Systems with procedures that assure the quality of every aspect of the trial should be implemented.

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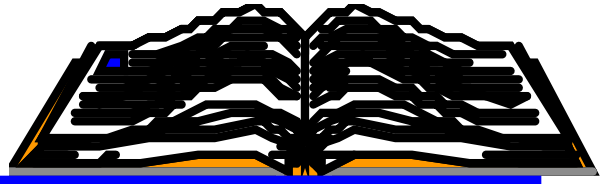
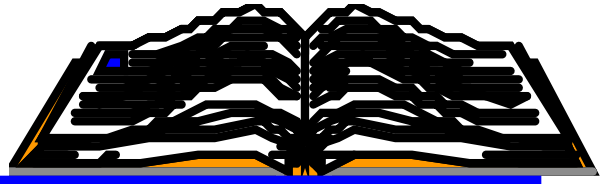


Good Clinical Practice

Factors:

Good cooperation between stakeholders



Good documentation

ICH-GCP defines roles and responsibilities of Key Stakeholders

Regulatory Authorities

The Sponsor

The Ethics Committees (IRB / IEC)

The Investigators

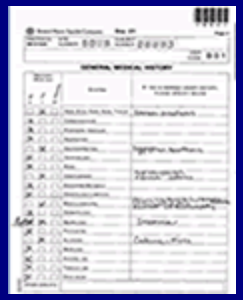
The Subjects

ICH-GCP defines quality standards of Essential Documents for clinical trials

Protocol

Investigator Brochure

Informed Consent Form



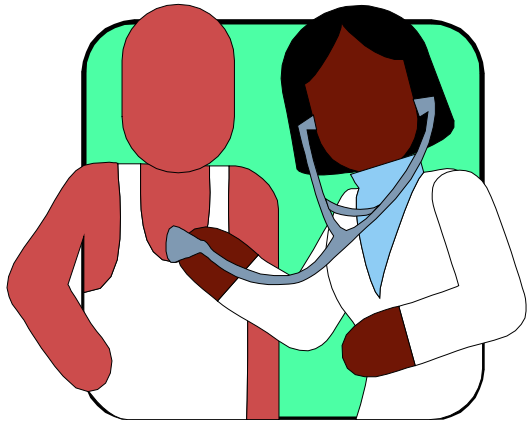
CRF

Source documents

ICH - Guideline for GCP

Compliance with this standard provides public assurance that:

- **Rights**, **safety**, and **well-being** of trial subjects are protected
- Clinical trial **data** are **credible**



Compliance to GCP is beneficial to all

Patient:

Investigator:

Sponsor:

Ethics Committee:

Regulatory Authorities:

Benefits of GCP for Stakeholders

Patient:	Protection of patients' rights, well-being, and safety
Investigator:	Improves scientific knowledge and opportunity for publications
Sponsor:	Clinical trial data are valid and credible
Ethics Committee:	Assurance that patient is well protected
Regulatory Authorities:	Assurance of safe and high quality drug

Benefits of GCP Training for Investigators

- Sponsor requirements/expectations are clear at study start
- Less time spending on corrections/problems during trial execution
- Quicker database closures = quicker time to publish
- Reputation as a compliant, efficient Clinical Investigators = funding opportunities

Benefits of GCP training for Sponsors

Well-trained staff

Improved control and execution of clinical trials

Less errors/problems to correct

Faster database closures

Faster time to market/faster time to abandon fruitless studies

Successful regulatory inspections

Reputation as a compliant company

Summary: ICH-GCP

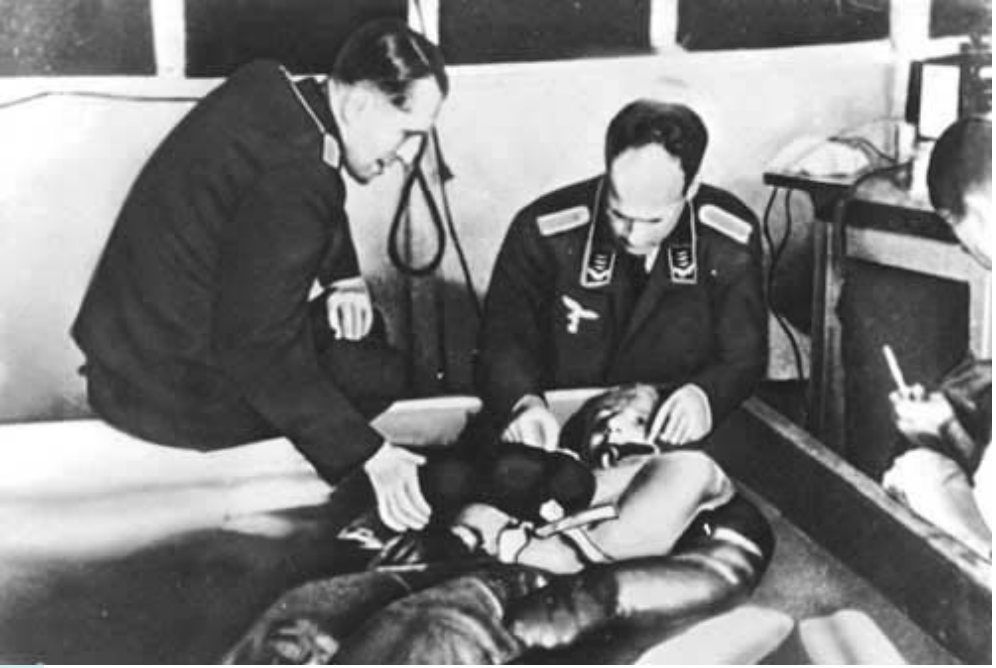
International Ethical/Scientific quality standards:

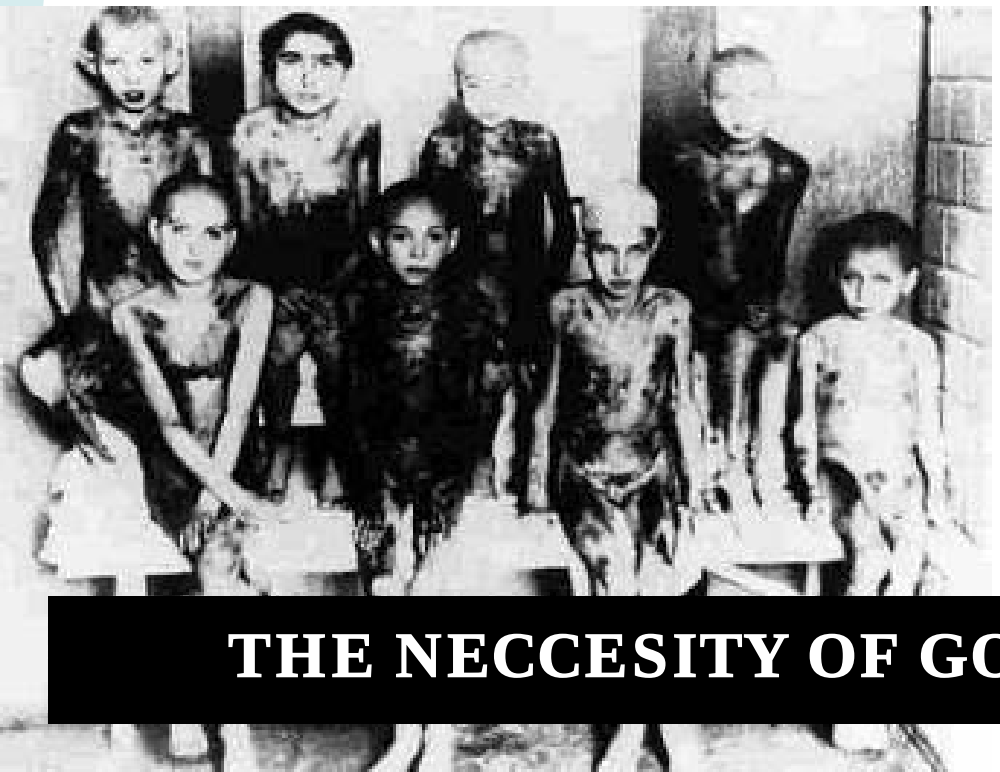
Clinical trials:
- Designing
- Conducting
- Recording
- Reporting

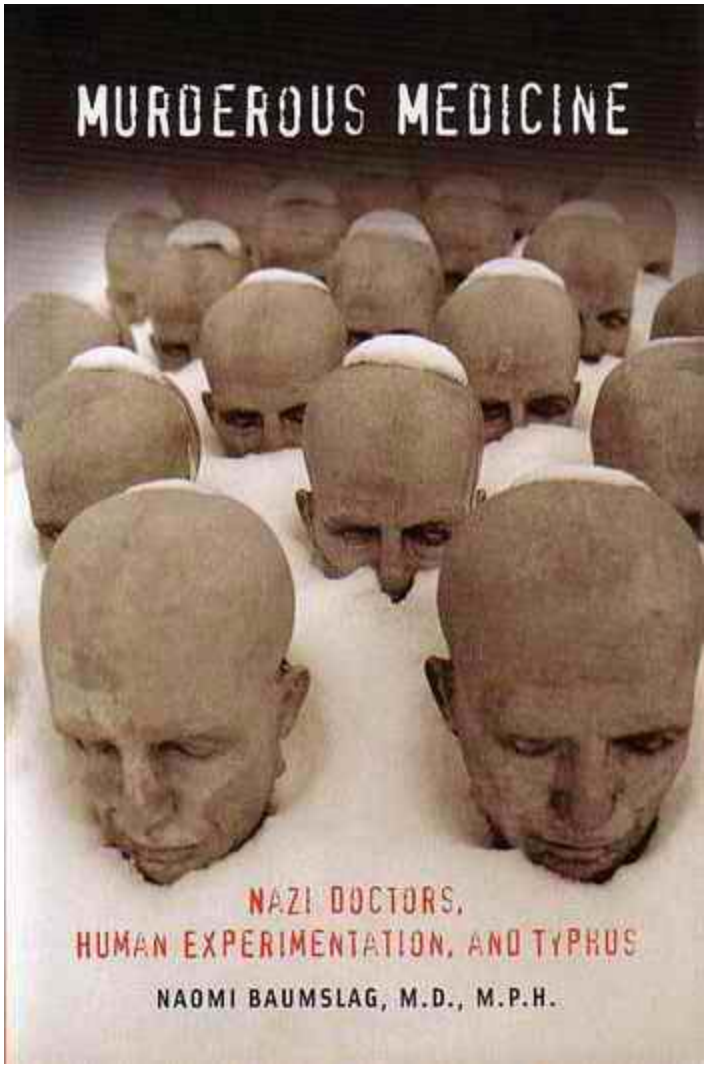
Compliance to GCP

Subjects:
- Rights
- Safety
- Well-being

Valid/credible clinical data







THE NECCESITY OF GOOD CLINICAL PRACTICE

Questions and Answers

GCP training overview:

What is appropriate Informed Consent ?

Who are the key 'players' in a clinical trial and who is responsible for what ?

What are the essential components of source documentation and CRF completion ?

Why is comprehensive investigational Drug accountability important?

What is the role of the Independent Ethics Committee in clinical research ?

Why is complete and accurate record keeping essential for a trial ?

Thank you


PRHMA
Pharmaceutical Research &
Manufacturers Association