The Life Raft GROUP

GENERICS Overview

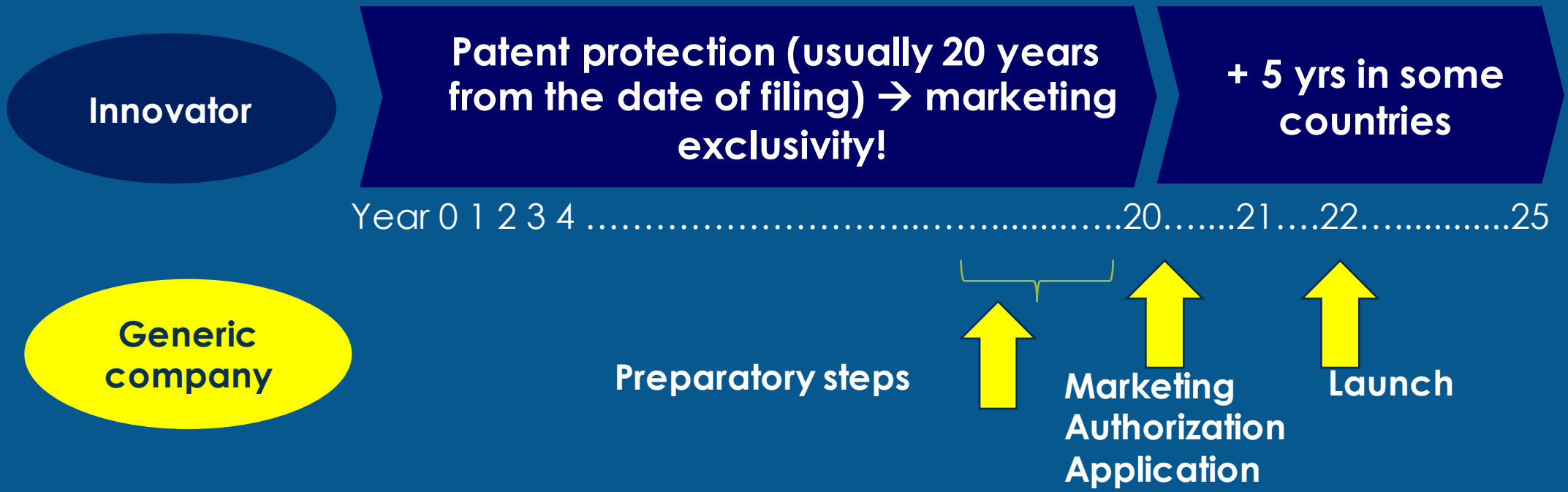
The Life Raft GROUP

TERMINOLOGY

- **Generic drug**
  - Product that is comparable to innovator drug product in dosage form, strength, route of administration, quality and efficacy, and intended use. Generic drug can only be marketed after patent & exclusivity protection ends.
- **Copy drug**
  - Drug provided by third party manufacturers despite the drug is still patented
- **Substandard drug**
  - A "genuine" drug product
  - Does not meet quality specifications
  - Due to difference in isoforms, isomers & impurities, may lead to lack of therapeutic equivalence
- **Counterfeit drug**
  - Deliberately and fraudulently mislabeled
  - Can apply to branded or generic drugs
  - Includes products with correct or wrong ingredients, without active ingredients, with insufficient active ingredients, with fake packaging

The Life Raft GROUP

WHEN & HOW DO GENERICS COME INTO PLAY?



The Life Raft GROUP

Drug Development and Approval Process (innovator product)

1 Pre-clinical

New Drug Development
- New?
- More effective?
- Less side effects?

Animal testing
- Toxicity, Damage, other cancers?

→ Drug ready for testing in humans

2 Clinical

Phase I study
- „first time in human“
- 20-80 healthy volunteers[1]

Phase II study
- 150-350 patients
- Toxicity, Safety

Phase III study
- 250-4000 patients
- Efficacy in comparison

→ Market-ready drug

3 Approval

Regulatory Approval
- Marketing Authorization (Application, Authorization)

Health Technology Assessment[2]
- Assessment of cost effectiveness

→ Drug ready to reach patients

4 Post-Marketing

Product launch

Post marketing surveillance:
- Phase IV studies
- Observational studies
- Adverse event monitoring
- Patient Registries
- …

→ Improve quality of health care

[1].Exception for cancer therapy: Late stage tumor patients included; [2].Selected countries only

The Life Raft GROUP

Generic Approval Process

1 Pre-clinical

New Drug Development

- New?
- More effective?
- Less side effects?

Animal testing

- Toxicity, Damage, other cancers?

→ Drug ready for testing in humans

2 Clinical

Phase I study

- „first time in human“
- 20-80 healthy volunteers[1]

Phase II study

- 150-350 patients
- Toxicity, Safety

Phase III study

- 250-4000 patients
- Efficacy in comparison

→ Market-ready drug

3 Approval

Regulatory Approval

- Marketing Authorization (Application, Authorization)

Health Technology Assessment[2]

- Assessment of cost effectiveness

→ Drug ready to reach patients

4 Post-Marketing

Product launch

Post marketing surveillance:

- Phase IV studies
- Observational studies
- Adverse event monitoring
- Patient Registries
- …

→ Improve quality of health care

[1] Exception for cancer therapy: Late stage tumor patients included; [2] Selected countries only

The Life Raft GROUP

EQUIVALENCE OF GENERICS: REGULATORY ASSUMPTION

Pharmaceutical Equivalence + **Bioequivalence** = **Therapeutic Equivalence**

Exemption from long and expensive Phase III studies

The Life Raft GROUP

SIMILARITIES & DIFFERENCES

In tightly regulated markets like EU or US, generic drugs are required to have:

- Same active ingredient, amount of active ingredient, purity
- Same pharmacokinetic & pharmacodynamic properties
- Same stability
- Same mechanism of action, safety & efficacy
- Same therapeutic indication & route of administration

What is allowed are…

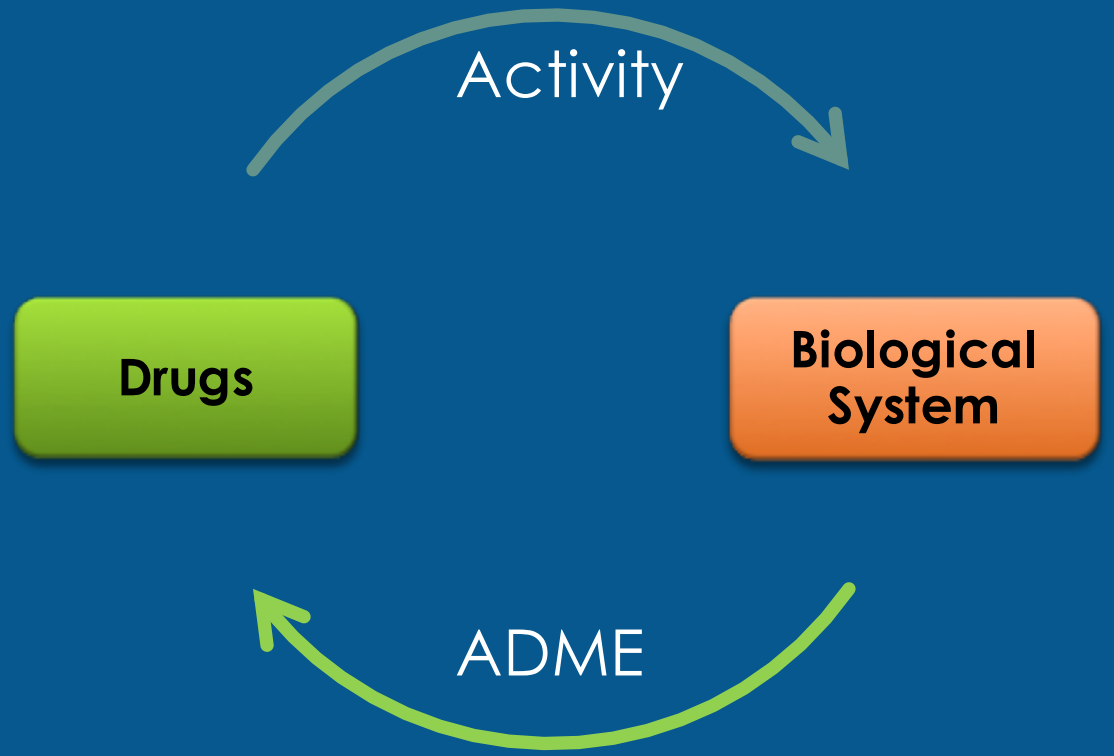
- Different salts
- Different excipients (colors, flavors, preservatives)
- Different shape, size and scoring
- Different product expiration
- Different manufacturing process
- Different product name & packaging

Note: For salts and excipients, unless they differ significantly in their safety and/or efficacy properties, the generic manufacturer has to submit further proof of efficacy and safety.

The Life Raft GROUP

Pharmacokinetics – what the body does to the drug

Pharmacodynamics – what the drug does to the body



The Life Raft GROUP

BIOAVAILABILITY AND BIOEQUIVALENCE

The Life Raft GROUP

BIOAVAILABILITY

Is the fraction/amount of administered drug that reaches the systemic circulation.

- Theory Basis: IV administration = 100% bioavailability
- Example: if 100 mg of a drug is administered orally and 70 mg of this drug is absorbed unchanged, the bioavailability is 70%
- Determined by comparing plasma levels of a drug after a particular route of administration (ex. Oral) with plasma drug levels achieved by IV injection.

The Life Raft GROUP

WHAT AFFECTS BIOAVAILABILITY?

Dosage-form related:

- Nature of the drug formulation
- Chemical instability
- Solubility of the drug
- First-pass hepatic metabolism

The Life Raft GROUP

WHAT OTHER FACTORS THAT AFFECT BIOAVAILABILITY?

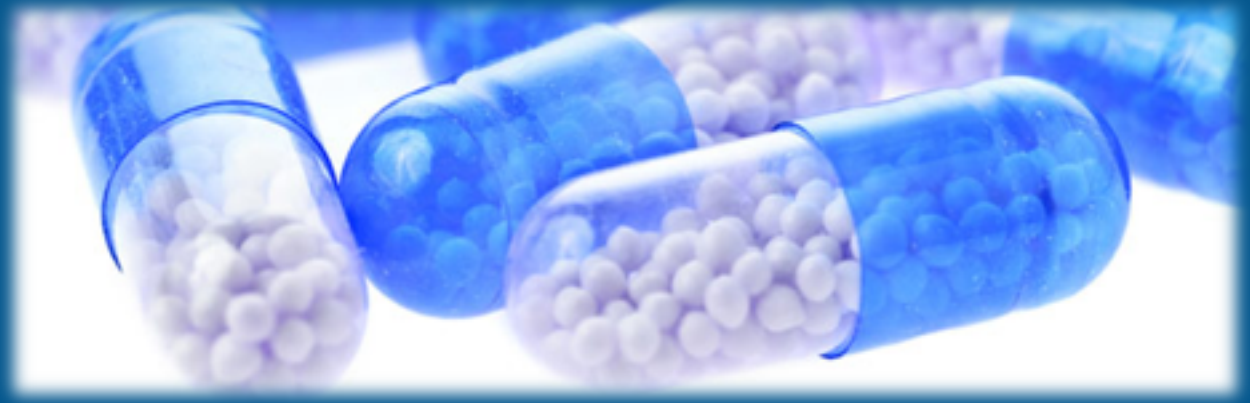
Patient Idiosyncrasy:

- Meals and timing
- Age
- Gender
- Disease
- Genetic traits
- GI physiology
- Others

The Life Raft GROUP

BIOEQUIVALENCE

- Two related drugs are bioequivalent if they show comparable bioavailability and similar times to achieve peak blood concentrations.
- Bioequivalent products can be substituted for each other without any adjustment in dose or other additional therapeutic monitoring



The Life Raft GROUP

HOW IS BIOEQUIVALENCE ASSESSED?

Bioequivalence studies are conducted in a small number of healthy (normal) adult volunteers.

Method: Single dose, two treatment, crossover designed pharmacokinetic study

Study number:

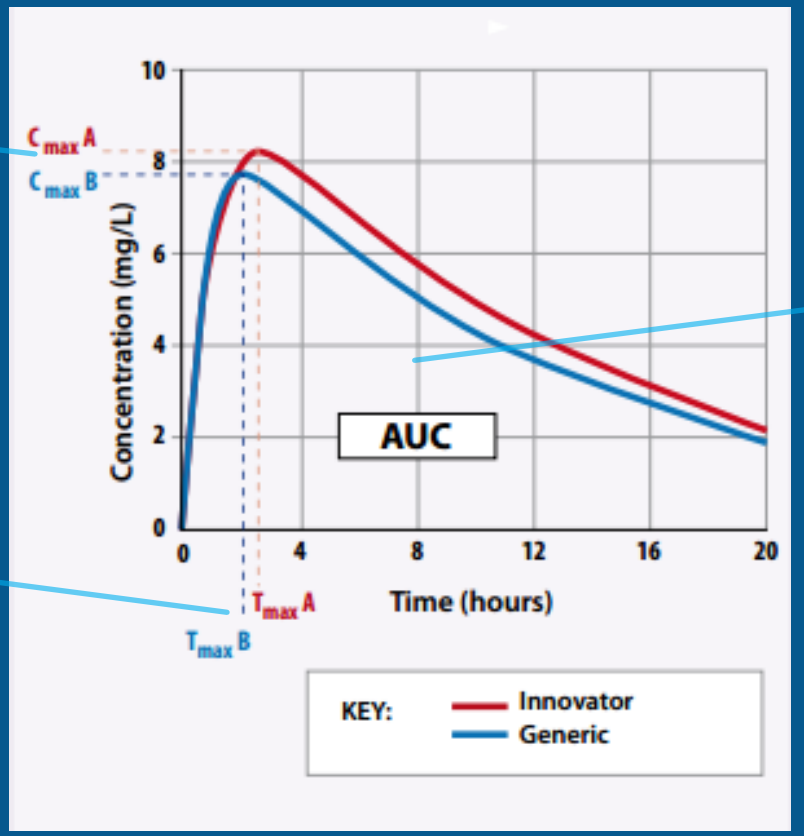
- US: 24-36
- Canada: 12
- WHO: 12

The Life Raft GROUP

BIOEQUIVALENCE STUDIES SHOW THAT ACTIVE INGREDIENT IN PATIENTS' BLOODSTREAM IS THE SAME IN GENERIC AND INNOVATOR PRODUCT

C_{max} - maximum plasma drug concentration

T_{max} - time required to reach maximum concentration



AUC - total area under the plasma drug concentration-time curve

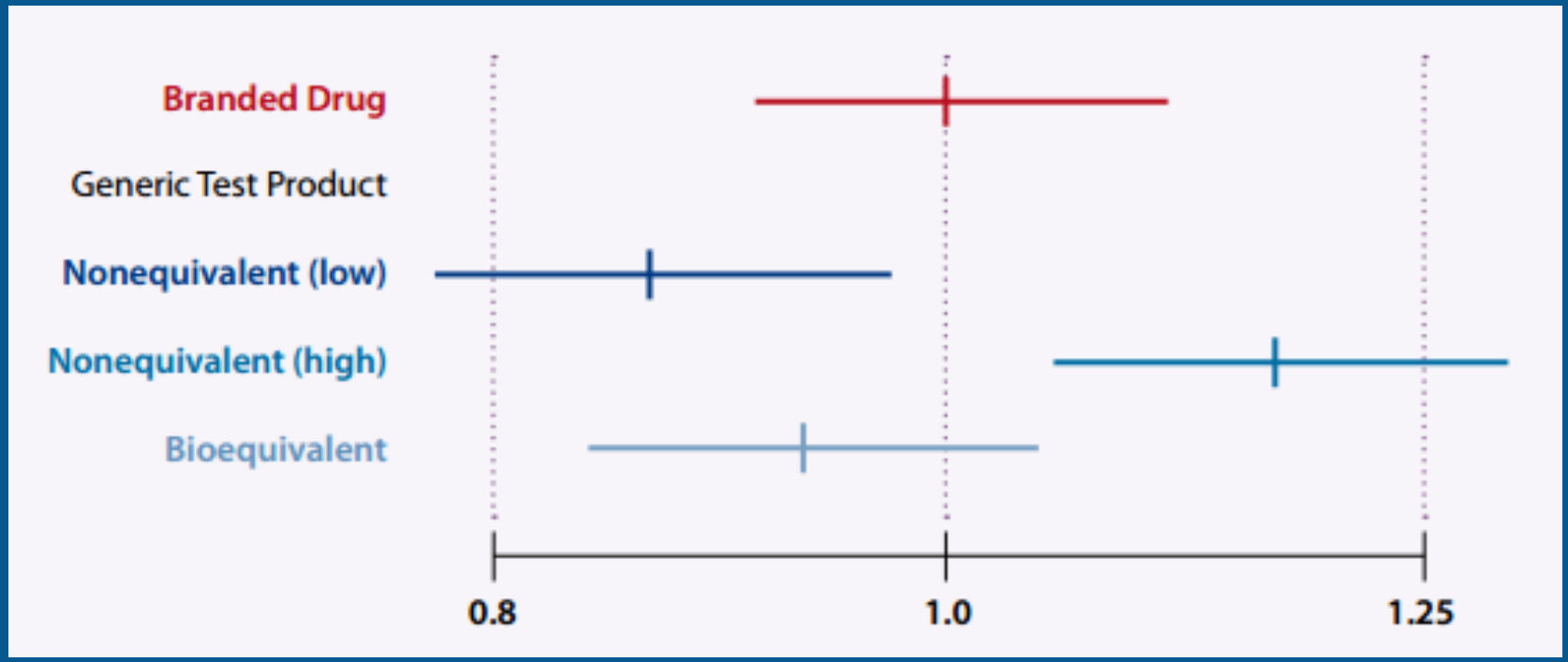
No significant difference between both products in terms of blood levels and time

Source: http://www.bpac.org.nz/magazine/2009/generics/docs/bpjse_generics_bio_pages_4-8.pdf

The Life Raft GROUP

HOW IS BIOEQUIVALENCE ASSESSED?

Criteria for acceptance: 90% confidence interval of the ratios of AUC, Cmax and Tmax fall between 80-125% or .80 and 1.25 (log-transformed data)



Source: http://www.bpac.org.nz/magazine/2009/generics/docs/bpjse_generics_bio_pages_4-8.pdf

The Life Raft GROUP

GENERIC GENERAL GUIDELINES

- Other than the active ingredient, a generic may contain different binders and fillers (inactive ingredients).
  - Ask you pharmacist for the package insert or use a searchable database like DailyMed
- Identify the manufacturer for the generic drug and ask for the same one at refill for consistent benefit.
- Find out if an "authorized" generic exists for your drug.
  - FDA Orange Book (US only)
- When switching to a generic, monitor your condition carefully. Report adverse events to the FDA or equivalent authority if outside the United States.

The Life Raft GROUP

Acknowledgement:

Thank you to Jan Geissler, Co-founder of the CML Advocates Network

The Life Raft Group

liferaft@liferaftgroup.org

973-837-9092

The Life Raft GROUP