GENERICS Overview
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
WHEN & HOW DO GENERICS COME INTO PLAY?

- Patent protection (usually 20 years from the date of filing) → marketing exclusivity!
- + 5 yrs in some countries

Preparatory steps: Marketing Authorization Application → Launch
## Drug Development and Approval Process (innovator product)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
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| **Pre-clinical** | New Drug Development  
- New?  
- More effective?  
- Less side effects?  
Animal testing  
- Toxicity, Damage, other cancers? |
| **Clinical** | Phase I study  
- „first time in human“  
- 20-80 healthy volunteers¹  
Phase II study  
- 150-350 patients  
- Toxicity, Safety  
Phase III study  
- 250-4000 patients  
- Efficacy in comparison |
| **Approval** | Regulatory Approval  
- Marketing Authorization (Application, Authorization)  
Health Technology Assessment²  
- Assessment of cost effectiveness |
| **Post-Marketing** | Product launch  
Post marketing surveillance:  
- Phase IV studies  
- Observational studies  
- Adverse event monitoring  
- Patient Registries  
- … |

¹ Exception for cancer therapy: Late stage tumor patients included; ² Selected countries only
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
   - Phase II study
     - 150-350 patients
     - Toxicity, Safety
   - Phase III study
     - 250-400 patients
     - Efficacy in comparison
   - Market-ready drug

3. Approval
   - Regulatory Approval
     - Marketing Authorization (Application, Authorization)
   - Health Technology Assessment
     - 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
EQUIVALENCE OF GENERICS: REGULATORY ASSUMPTION

Exemption from long and expensive Phase III studies
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.
Pharmacokinetics – what the body does to the drug

Pharmacodynamics – what the drug does to the body

Pharmacodynamics

Activity

Drugs

Biological System

ADME

Pharmacokinetics
BIOAVAILABILITY AND BIOEQUIVALENCE
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.
WHAT AFFECTS BIOAVAILABILITY?

Dosage-form related:

- Nature of the drug formulation
- Chemical instability
- Solubility of the drug
- First-pass hepatic metabolism
WHAT OTHER FACTORS THAT AFFECT BIOAVAILABILITY?

Patient Idiosyncrasy:
- Meals and timing
- Age
- Gender
- Disease
- Genetic traits

- GI physiology
- Others
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.
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
BIOEQUIVALENCE STUDIES SHOW THAT ACTIVE INGREDIENT IN PATIENTS’ BLOODSTREAM IS THE SAME IN GENERIC AND INNOVATOR PRODUCT

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

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)

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.
Acknowledgement:

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