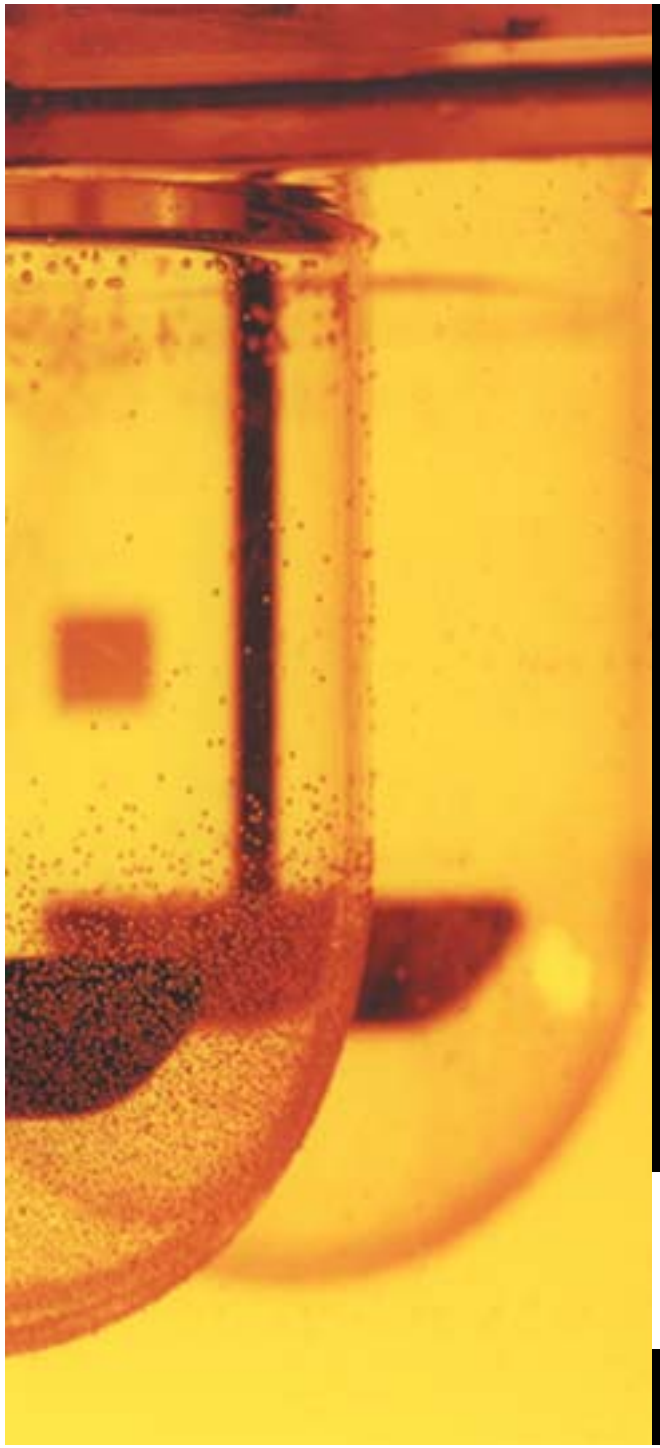

Bioavailability and Bioequivalence

IKEV / APV Conference Istanbul April 5-16, 2004

Introduction

Dr. Johannes Krämer

PHAST Pharmaceutical Quality Standards

What is a Generic Drug?

A generic drug is bioequivalent to a brand name drug in dosage form's

- safety
- strength
- route of administration
- quality
- performance characteristics
- intended use

Sold at substantial discounts from the branded drug's price

http://www.accessdata.fda.gov/scripts/cder/iig/index.cfm

provides information about

- **Inactive Ingredient**
  - An inactive ingredient is any component of a drug product other than the active ingredient. Only inactive ingredients in the final dosage forms of drug products are included in this database.
- **Route**
  - A route of administration is a way of administering a drug to a site in a patient.
- **Dosage Form**
  - A dosage form is a form in which a drug is produced and dispensed.

Generic Drugs Approved by FDA in March 2004

1	METOLAZONE TABLETS, USP 5 MG
2	CHLORHEXIDINE GLUCONATE ORAL RINSE, USP 0.12%
3	LORATADINE AND PSEUDOEPHEDRINE SULFATE EXTENDED-RELEASE TABL 10 MG/240 MG (24-HOUR FORMULATION) (OTC)
4	PAROXETINE HYDROCHLORIDE TABLETS 10 MG (BASE), 20 MG (BASE), 30 MG (BASE), AND 40 MG (BASE)
5	PAROXETINE HYDROCHLORIDE TABLETS 10 MG (BASE), 20 MG (BASE), 30 MG (BASE) AND 40 MG (BASE)
6	PHENYTOIN ORAL SUSPENSION, USP 125 MG/5 ML
7	OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS 80 MG
8	AMOXICILLIN & CLAVULANATE POTASSIUM FOR ORAL SUSPENSION, US 600 MG/42.9 MG (BASE)/5 ML
9	HYDROCORTISONE CREAM, USP 2.5% VINTAGE PHARMACEUTICALS, LLC
10	NAPROXEN SODIUM & PSEUDOEPHEDRINE HCL EXTENDED-RELEASE TABLE 200 MG (BASE)/120 MG
11	DEFEROXAMINE MESYLATE FOR INJECTION, USP 500 MG/VIAL AND 2 G/VIAL
12	PROMETHAZINE HYDROCHLORIDE INJECTION, USP 25 MG/ML AND 50 MG/ML PACKAGED IN 1 ML AMPULES
13	DICLOFENAC POTASSIUM TABLETS 50 MG
14	HYDROCODONE BITARTRATE AND IBUPROFEN TABLETS 5 MG/200 MG
15	OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS 10 MG, 20 MG, AND 40 MG
16	COLISTIMETHATE FOR INJECTION, USP 150 MG (BASE)/VIAL PADDOCK LABORATORIES, INC.
17	CLINDAMYCIN HYDROCHLORIDE CAPSULES, USP 150 MG (BASE), AND 300 MG (BASE)
18	NITROFURANTOIN (MONOHYDRATE/MACROCRYSTALS) CAPSULES 100 MG
19	DEMECLOCYCLINE HYDROCHLORIDE TABLETS, USP 150 MG AND 300 MG
20	NIFEDIPINE EXTENDED-RELEASE TABLETS, USP 90 MG
21	NORGESTIMATE AND ETHINYL ESTRADIOL TABLETS 0.18 MG/0.035 MG, 0.215 MG/0.035 MG, AND 0.25 MG/0.035 MG PACKAGED AS A TRIPHASIC REGIMEN (28-DAY CYCLE)
22	FUROSEMIDE TABLETS, USP 20 MG, 40 MG, AND 80 MG
23	MICONAZOLE NITRATE SUPPOSITORIES & MICONAZOLE NITRATE CREAM 100 MG/2% (COMBINATION PACKAGE) (OTC)
24	ERYTHROMYCIN AND BENZOYL PEROXIDE TOPICAL GEL, USP 3%/5%
25	MICONAZOLE NITRATE CREAM 4% & MICONAZOLE NITRATE CREAM 2% 4%/2% (COMBINATION PACKAGE) (OTC)
26	QUINAPRIL HYDROCHLORIDE & HYDROCHLOROTHIAZIDE TABLETS 10 MG (BASE)/12.5 MG, 20 MG (BASE)/12.5 MG, AND 20 MG (BASE)/25 MG
27	CLINDAMYCIN PHOSPHATE TOPICAL SOLUTION, USP 1% (BASE)

How to Register Generics in the US

- when patents expire manufacturers an apply to the FDA
- companies must submit an ANDA

  (Abbreviated New Drug Application)
- ANDA does not include:
  - animal studies
  - therapeutic studies
- ingredients and dosage forms already proved for safety and efficacy
- applies to drugs first marketed after 1962

US FDA’s Office of Generic Drugs Requirements

To gain FDA approval, a generic drug must:

- contain the same active ingredients as the innovator drug (inactive ingredients may vary)
- be identical in strength, dosage form, and route of administration
- have the same use indications
- be bioequivalent
- meet the same batch requirements for identity, strength, purity, and quality
- be manufactured under the same strict standards of FDA's good manufacturing practice regulations required for innovator products

Bioequivalence – A Two Dimensional Approach

within one product

- from predecessor to actual formulation

between two or more (multisource) products

- concept of interchangeability without modification of dosing scheme

CTM –Timeline / Months

-9	-6	-3	0	+1
Plan / Schedule Labor Facilities Contractor	Materials Inactive Materials API Container/Closure Spec‘s Order/Receive Sample Test release	Manufacturing Process Formulation IP Control Cleaning Methods Analytical Methods Specifications Testing / Rlease Batch Records Stability Expiry Period	Other Materials Ancillary Supplies Concomitant Medication Package Design	GMP Aprovals Shipping Approval Shipping
Plan Clinical Trial Design and Order Required Product Qaulities and Strengths		Provide Draft of Cljnical Protocol and Statistics Criteria	Provide Final Draft of Clin. Protocol Agree on Package Design, Agree on Delivery Date Establish Contratcs with CRO	Receive Supply Inititae Clinical Trial

modified from Carney C.F., Pharm. Engineering, Sept/Oct 2003

Bioavailability Studies Always Needed?

- formerly used positive list of German BfArM obsolete. Gave clear advise when Be studies where required.
- modern approach by IBCSDAB-work:

  - D.M. Barends
  - G. Amidon
  - H.E. Junginger
  - K.K. Midha
  - V.P. Shah
  - J. Welink
  - H. Moeller
  - E. Stippler
  - H. Potthast
  - G. Jay
  - M. Olling
  - H. Vogelpoel
  - A. Schaeffler……..

The Program – Day 1

Day 1

- BA/BE Studies a a Surrogate for Clinical Investigations, Dr. Rettig
- Biopharmaceutical Classification System –Dissolution Testing a a Surrogate for BE Studies, Dr. Barends
- Dissolution Testing as a Surrogate for Bio-Studies, Dr. Krämer
- Quality of Clinical Trial Material to be Tested in Man, Dr. Krämer
- Physiologically Meaningful Dissolution Testing, Dr. Krämer

The Program – Day 2

Day 2

- Pharmacokinetic Analysis and Biometric Evaluation, Dr. Rettig
- Design and Validation of Bioanalytical Test Methods, Dr. Krämer
- Special Aspects of BA/BE testing, Dr. Rettig
- General Discussion on BA/BE Testing and / or Data Processing, all speakers
- Role of IVIVC in BA/BE Strategies for Product Development, Dr. Rettig

- General Discussion, all speakers