Part I
Bioequivalence Testing: Background and History

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Outline

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- Data for bioequivalence testing
- Experimental designs
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In an equivalence trial, the aim is to show that two treatments are not too different in characteristics

Not too different: to be appropriately defined.

Background

New drug: approved by the US Food and Drug Administration (FDA)

Complicated approval process by the US FDA

Company has exclusive rights to sell the brand name drug for a number of years (patent period)

Brand name drug could be expensive

Once the patent runs out, others can copy the brand name drug

Generic drug: a copy of the brand name drug

Approval process is simple for generic drugs.

Enough to show that a generic drug is equivalent to a brand name drug

Show that the concentration of the active ingredient that enters the blood is similar for the generic drug and the brand name drug

Called bioequivalence testing

Generic drugs: much cheaper

Bioequivalence testing can also be used to compare different forms of the same drug: tablet, capsule, solution, powder, intra-vascular etc.

Lipitor: Cholesterol lowering medication by Pfizer.

Was the top selling drug in the world for a number of years.

Sales for 2010: $10.7 billion

Canadian and Spanish patents expired in 2010.

Sales for 2011: $9.6 billion

U.S patent expired on November 30, 2011

Sales for 2012: $3.9 billion

Generic versions by several companies are now available

Sales for 2018: $2.1 billion

Humira: anti-inflammatory drug manufactured by AbbVie Pharmaceuticals

December 31, 2002: Humira approved by the U.S. FDA

Currently the world's top selling drug

2017 sales: $18.4 billion

2018 sales: $19.9 billion

European patent expired in 2018

US patent was supposed to expire in December 2016

AbbVie went to court and secured more than 100 additional patents covering things such as manufacturing methods and the drug's formulation.

The patent period was extended: a generic version cannot be sold in USA until 2023.

Humira costs approximately $1,000 for a vial

Exemptia, a generic copy available in India since 2015, costs $200

Lipitor is a chemical drug.

Humira and Exemptia are not chemical drugs.

Humira and and Exemptia are examples of biological drug products or biologics.

Manufacture of Humira involves:

Providing a host cell that is genetically engineered to express two specific amino acid sequences ....

Culturing the host cell under conditions whereby the cell expresses the first and second amino acid sequences, wherein the expressed first and second amino acid sequences form recombinant antibodies ...

Harvesting the recombinant antibodies from the host cell culture to produce an antibody preparation .....

A generic version of a biologic (such as Humira) is called a biosimilar.

Biological availability, or *bioavailability* of a drug: the rate and extent to which the active drug ingredient is absorbed into the blood, and becomes available at the site of drug action.

Two drug products are *bioequivalent* if they have similar rate and extent of absorption into the blood.

Two drug products are *therapeutically equivalent* if they provide similar therapeutic effects.

Fundamental bioequivalence assumption: If two drug products are bioequivalent, they are also therapeutically equivalent.

History

During the early 1970's, the U.S. Congress passed the *Drug Price Competition and Patent Term Restoration Act* that authorized the FDA to approve generic drug products.

The "Hatch-Waxman Act"

The American Statistical Association then formed a *Bioavailability Committee* to establish statistical procedures for establishing bioequivalence.

The statistics community was involved right from the beginning!

Under the Drug Price Competition and Patent Term Restoration Act, the FDA was authorized to approve generic drug products in 1984.

A *Bioequivalence Task Force* was formed in 1986 to examine the FDA's procedures for approving generic drug products.

The Task Force released their report in January 1988, and several statistical issues were pointed out.

In 1992, the FDA issued the guidance on statistical procedures for establishing bioequivalence.

A revised guidance document was issued in 2001 and later in 2013.

New Drug Application (NDA): Required to get a new drug approved

Abbreviated New Drug Application (ANDA): Required to get a generic drug approved.

Generic drug applications are termed **abbreviated** because they are generally not required to include preclinical (animal) and clinical (human) data to establish safety and effectiveness.

Instead, generic applicants must scientifically demonstrate that their product is bioequivalent (i.e., performs in a similar manner as the original drug).

Data for bioequivalence testing

An example:

Mysoline: a brand name drug used for treating epilepsy

Primidone: the active ingredient in Mysoline

(**www.epilepsyfoundation.org**)

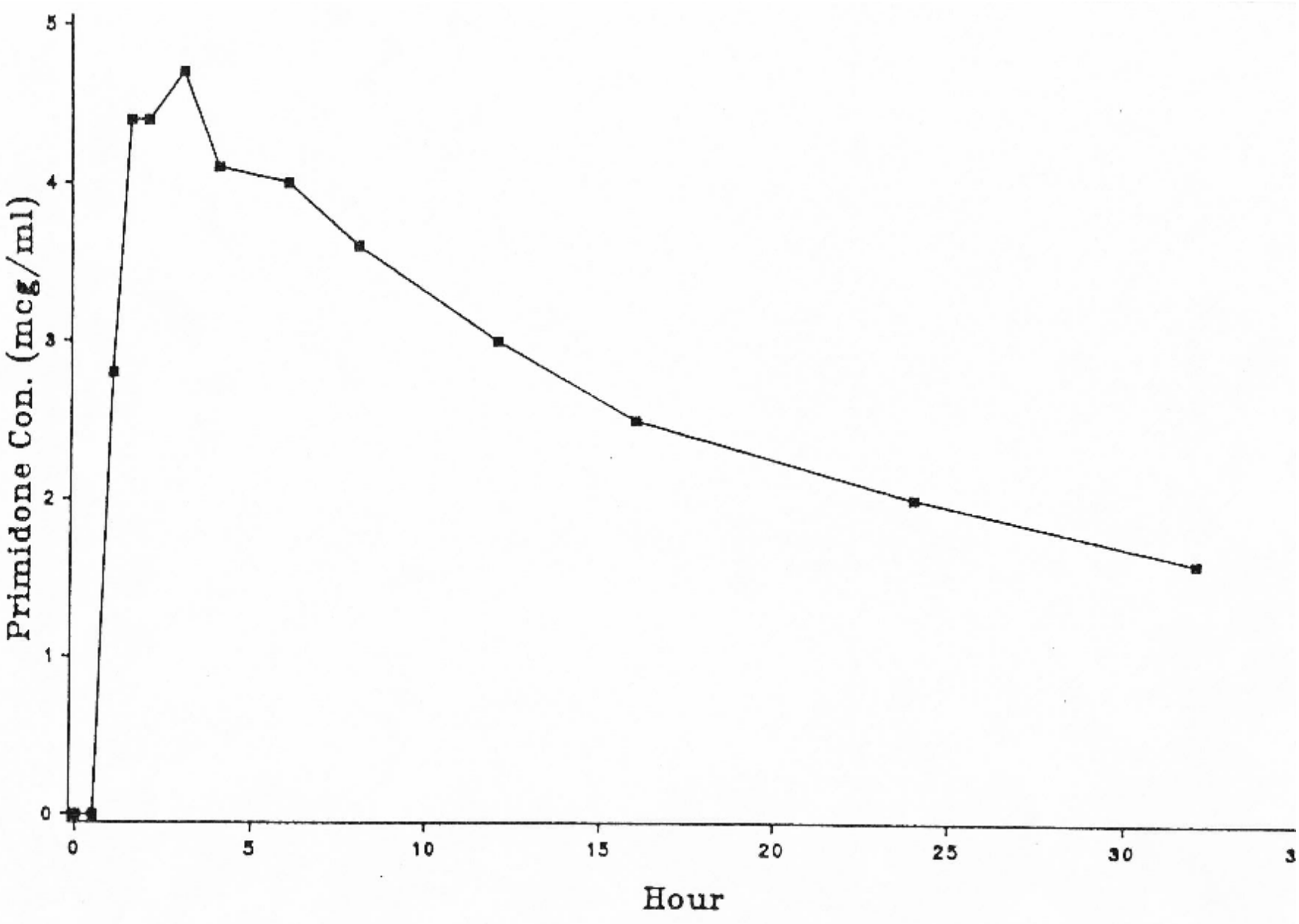
A subject receives 250-mg tablet of primidone

Measure the concentration of primidone (micrograms/ml) in the blood several times, over a 32 hour period

Plot the data against time

Primidone concentration in the blood of one subject:

Blood Sample	Time	Concentration
1	0.0	0.0
2	0.5	0.0
3	1.0	2.8
4	1.5	4.4
5	2.0	4.4
6	3.0	4.7
7	4.0	4.1
8	6.0	4.0
9	8.0	3.6
10	12.0	3.0
11	16.0	2.5
12	24.0	2.0
13	32.0	1.6



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Data obtained from healthy volunteers (male and female)

18-55 years old, BMI = 18-25 kg/m^2

Non-smokers/without a history of alcohol or drug abuse

Medical history/Clinical Lab test values must be within normal ranges

Other criteria .....

If two drug products perform the same in healthy volunteers, the assumption is made that they will perform the same in patients with the disease.

Data obtained on three variables:

Area under the curve (AUC)

Maximum blood concentration (C_{max})

Time to reach the maximum concentration (T_{max})

AUC: extent of bioavailability

C_{max}: rate of bioavailability

Statistical analysis of the data is done to determine if the two drugs are equivalent.

AUC and C_{max}: often lognormally distributed.

For the primidone data for one subject,
$C_{max} = 4.7$ micrograms/ml, $T_{max} = 3$ hours.

Is it enough to reduce the data to just three measures?

Pharmacokinetic theory says so.

Experimental designs

Mysoline: reference drug (R)

Generic drug: test drug (T)

Each subject receives both R and T, separated by a **washout period**

Crossover designs are used

A two sequence–two period crossover design:

	Period	
Sequence	I	II
1	R	T
2	T	R

A two sequence−four period crossover design:

	Period			
Sequence	I	II	III	IV
1	T	T	R	R
2	R	R	T	T

A four sequence−four period crossover design:

	Period			
Sequence	I	II	III	IV
1	T	T	R	R
2	R	R	T	T
3	T	R	R	T
4	R	T	T	R

Univariate bioequivalence testing: Based on the separate modeling and analysis of the univariate responses AUC, C_{max} and T_{max}.

Multivariate bioequivalence testing: Based on the joint modeling and analysis of all the three responses AUC, C_{max} and T_{max}, or any two of them (typically, AUC and C_{max}).

Usually log-transformed data are analyzed.

If a drug is being copied, why is bioequivalence testing necessary? Aren't they automatically equivalent?

Generic drugs are required to contain the same active ingredient as the original brand name drug.

The additional ingredients, known as **excipients**, can be different

Such differences can affect the amount of drug that could potentially be absorbed into the bloodstream.

This can result in drugs that release active ingredients into the blood far more quickly, or far more slowly.

The importance of T_{max}!

In September 2012, the FDA withdrew approval for an earlier generic version of the anti-depressant drug Wellbutrin.

In April 2014, the FDA withdrew approval for a second generic version of Wellbutrin.

Reason: the active ingredient was released too quickly into the blood.

Commentary by Derek Lowe: "The Generic Wellbutrin Problem: Whose Fault Is It?" Appeared in *Science Translational Medicine*, October 18, 2012.

Blog by Katherine Eban: " Are generics really the same as branded drugs?" Appeared in *Fortune*, January 10, 2013.

Bioequivalence criteria

Average bioequivalence

μ_T, μ_R: average responses among the population of patients who will take the test drug, and the reference drug, respectively.

The response is usually AUC, after log-transformation (could be C_{max} or T_{max}).

Average bioequivalence holds if μ_T and μ_R are equivalent, i.e., they are "close"

Equivalence is not the same as equality.

μ_T and μ_R are considered equivalent if $|\mu_T - \mu_R| < \ln(1.25)$.

After obtaining data from a crossover design, perform a statistical test to decide if $|\mu_T - \mu_R| \geq \ln(1.25)$ or if $|\mu_T - \mu_R| < \ln(1.25)$

Hypotheses to be tested

$$H_0 : \ |\mu_T - \mu_R| \geq \ln(1.25) \ \text{ versus } \ H_1 : \ |\mu_T - \mu_R| < \ln(1.25)$$

Conclude average bioequivalence if H_0 is rejected after a statistical test based on the log-transformed AUC data.

Where did the constant ln(1.25) come from?

Recall that μ_T and μ_R are population means based on the log-transformed data.

If $\theta_T = \exp(\mu_T)$ and $\theta_R = \exp(\mu_R)$, then θ_T and θ_R are on the original scale.

Thus $\frac{\theta_T}{\theta_R}$ is a scale free quantity.

Consider θ_T and θ_R to be equivalent if the scale free quantity $\frac{\theta_T}{\theta_R}$ is around one.

The limits to be used are usually taken to be 0.80 and 1.25

That is, declare θ_T and θ_R to be equivalent if $0.80 < \frac{\theta_T}{\theta_R} < 1.25$.

Since $\theta_T = \exp(\mu_T)$ and $\theta_R = \exp(\mu_R)$, taking logarithm, we get

$$\ln(0.80) < \mu_T - \mu_R < \ln(1.25)$$

Equivalent to $|\mu_T - \mu_R| < \ln(1.25)$ since $\ln(0.80) = -\ln(1.25)$.

Why does the same constant ln(1.25) make sense in every problem?

Since $\frac{\theta_T}{\theta_R}$ is scale free, $\mu_T - \mu_R = \ln\left(\frac{\theta_T}{\theta_R}\right)$ is also scale free

Thus the same constant ln(1.25) can be used to test the equivalence of μ_T and μ_R.

Univariate average bioequivalence hypotheses:

$$H_0 : \ |\mu_T - \mu_R| \geq \ln(1.25) \ \text{ versus } \ H_1 : \ |\mu_T - \mu_R| < \ln(1.25)$$

Multivariate average bioequivalence:

Data on (AUC, C_{max}, T_{max})$'$ will be used for bioequivalence testing, perhaps after a log-transformation .

$\boldsymbol{\mu}_T$, $\boldsymbol{\mu}_R$: average responses on (AUC, C_{max}, T_{max})$'$, among the population of patients who will take the test drug, and the reference drug, respectively.

Write $\boldsymbol{\mu}_T - \boldsymbol{\mu}_R = \boldsymbol{\mu} = (\mu_1, \mu_2, \mu_3)'$.

The mean vectors $\boldsymbol{\mu}_T$ and $\boldsymbol{\mu}_R$ are equivalent if each component of $\boldsymbol{\mu} = \boldsymbol{\mu}_T - \boldsymbol{\mu}_R$ is equivalent to zero.

$$
\begin{aligned}
& H_0 : |\mu_1| \geq \ln(1.25) \text{ or } |\mu_2| \geq \ln(1.25) \text{ or } |\mu_3| \geq \ln(1.25) \\
\text{vs} \quad & H_1 : |\mu_1| < \ln(1.25),\ |\mu_2| < \ln(1.25) \text{ and } |\mu_3| < \ln(1.25)
\end{aligned}
$$

We conclude multivariate average bioequivalence if H_0 is rejected.

Other criteria

Several other criteria are available as part of bioequivalence assessment.

Variance bioequivalence: test if a ratio of variances is around one.

Average bioequivalence and variance bioequivalence use moment-based criteria.

Probability based criteria are also available in the literature.

A probability based criterion

Suppose Y_T and Y_R are random variables denoting the log-transformed responses to T and R from the same subject in a cross-over design.

Declare T and R to be equivalent if

$$\theta = P(|Y_T - Y_R| \leq \epsilon)$$

is large, for a suitably chosen ϵ.

Thus consider the following hypotheses:

$$H_0 : \ \theta \leq \theta_0, \ \text{vs} \ H_1 : \ \theta > \theta_0,$$

for a specified θ_0.

Declare bioequivalence if H_0 is rejected.

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Biosimilars

A new area of research

Unlike chemical drugs, biological products or medicines (biotechnology drugs or biologics) are therapeutic agents that are produced using a living system or organism.

Generic drugs are manufactured by chemical synthesis. Biologics are made of living cells or organisms

Biosimilar: A generic version of a biotechnology drug.

Humira is a biotechnology drug

Challenging to establish equivalence or similarity

Unlike the more common chemical drugs, biotechnology drugs generally exhibit high molecular complexity.

May be very sensitive to small changes during the manufacturing process, which will have an impact on the clinical outcome

The manufacturer of a generic copy does not have access to the originator's molecular clone and original cell bank, nor to the exact fermentation and purification process, nor to the active drug substance.

They have access only to the commercialized brand name product.

Differences in impurities and/or breakdown products can have serious health implications.

Because no two cell lines, developed independently, can be considered identical, biotech medicines cannot be fully copied

This has created a concern that copies might perform differently than the original branded version of the product.

Batch-to-batch variability is a major concern.

Different terms are used:

European Medicines Agency: Biosimilar

US FDA: Follow-on biologic (FOB)

WHO: Similar biotherapeutic product (SBP)

Health Canada: Subsequent-entered biologics (SEB)

The Biologics Price Competition and Innovation Act of 2009 (BPCI Act) was originally sponsored and introduced in 2007 by Senator Kennedy.

It was formally passed under the Patient Protection and Affordable Care Act, signed into law by President Obama on March 23, 2010.

The BPCI act is similar to the Drug Price Competition and Patent Term Restoration Act of 1970, and it creates an abbreviated approval pathway for biosimilars.

The BPCI Act defines a biosimilar product as a biological product that is highly similar to the reference drug product.

BPCI Act does not explain what is meant by highly similar

The Act does not provide any criteria for assessing biosimilarity

Check similarity of means and similarity of variances?

Separately, or jointly?

Can think of different criteria.

The European Medicines Agency (EMEA) has approved biosimilar versions of several drugs

The EMEA has reached the conclusion that there is no standard procedure that can be applied in order to approve a biosimilar

The guidelines are product-specific, and stop short of providing precise equivalence margins.

If comparison is made based on the concept of average bioequivalence only, the criterion does not take into consideration the variability, which is known to have a significant impact on clinical performance of biosimilars.

U.S. FDA released guidance documents in 2015 and 2016.

For biotechnology drugs with a short half-life, FDA (2016) recommends crossover designs for assessing biosimilarity.

For biological products with a higher half-life, parallel study designs are recommended.

The criterion suggested in the FDA (2016) document for the assessment of biosimilarity is the same criterion used for assessing average bioequivalence, namely the TOST.

Several researchers have expressed concerns about possible differences in variabilities that could affect the performance of biosimilars.

"How biosimilars are approved and how we use biosimilars will need to balance considerations of cost and development time with the possibility of variation in biological response." Patel et al. (*Journal of Dermatological Treatment*, 2015).

The non-availability of biosimilar versions of insulin has been an active topic of discussion in the literature.

Biosimilar versions of insulin are still not available; variability among batches has been a major concern; Heinemann et al. (*Diabetes, Obesity and Metabolism*, 2015).

"Manufacturers of biologics must also ensure that the batch-to-batch variability associated with every biological drug meets the required quality standards." DeVries et al. (*Diabetes, Obesity and Metabolism*, 2015).

Beran, D., Ewen, M. and Laing, R. (2016).Constraints and challenges in access to insulin: a global perspective. *The Lancet Diabetes & Endocrinology*, 4, 275-285.

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"Generics have not affected the insulin market..... Although the reasons behind this are not entirely clear, one distinction is that insulin is a biological product ..... The proof of similarity and the production process are more complicated for biologics."

Call to action: "Development of a regulatory framework for biosimilars and insulin, that ensures access to quality-assured, safe, efficacious, and costeffective insulin."

The European Medicines Agency almost approved a biosimilar version of insulin manufactured by Marvel Life Sciences, a generic company from India.

The approval was later withdrawn based on several concerns.

A major concern was that Marvel Life Sciences used only a single batch of insulin in their biosimilarity study.

The EMA (2008, p. 7) report notes that "This characterisation study is not sufficient since an extensive comparability exercise is required for a biosimilar product, which should include several batches each of the Marvel insulin Drug Substance and the claimed comparator insulin."

EMA (2008). Withdrawal assessment report for insulin human rapid marvel. Available at http://www.ema.europa.eu

Need to develop biosimilarity criteria that takes into account variabilities between and within batches.

In conclusion, much remains to be done for the assessment of biosimilarity.

On March 6, 2015, U.S. FDA approved the first biosimilar product Zarxio, manufactured by Sandoz.

Zarxio is a biosimilar version of Neupogen, manufactured by Amgen.

Neupogen helps the body make white blood cells after receiving cancer medications. Can also improve survival in people who have been exposed to radiation.

US FDA has so far approved several biosimlars.

A generic version of Humira, known as Amjevita, was approved on September 23, 2016.

However, Amjevita cannot be sold in USA until 2023!

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www.biosimilars.com: Site with substantive information about biosimilars

Biotechnology Information Institute (www.bioinfo.com)

Generics and Biosimilars Initiative Online (www.gabionline.net)

https://www.biosimilardevelopment.com/

A site launched in 2015 to provide information on all aspects of biosimilar development: regulatory guidelines, policy matters, and commercialization advances in the global biosimilar industry.