[S-9]

GLP Perspectives of Bioequivalence Studies

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Bioequivalence is a term in pharmacokinetics used to access the expected in vivo biological equivalence of two proprietary preparations of a drug. Bioequivalence studies are usually performed for generic drugs. Two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent and their bioavailabilities after administration in the same molar dose are similar. Bioequivalence is usually accessed by single dose in vivo studies in healthy volunteers and the reference product is usually the innovator product that is marketed. Regulatory definition of bioequivalence is based on the statistical analysis of thebioavailability of the reference and test product. In general, two products are evaluated as bioequivalent if the 90% confidence interval of the relative mean Cmaxand AUC of the test to reference product are within 80.00% to 125.00% in the fasting state. Key process in bioequivalence study is development and validation of bioanalytical method, determination of the drug concentration in the biosamples (usually plasma or serum) obtained from volunteers, calculation of the pharmacokinetic parameters and statistical analysis of the pharmacokinetic parameters. Although current guidelines and regulations do not require the bioequivalence studies to be done under good laboratory practice (GLP), the issues to perform the bioequivalence studies under GLP environment is emerged both from the regulatory and industry side. GLP perspectives of bioequivalence studiesare needed to be discussed in respect to achieve quality assurance in bioequivalence studies.

GLP Perspectives of Bioequivalence Studies

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Introduction of Bioequivalence (BE) Study

의약품 허가절차

Bioequivalence (BE)

- **Bioequivalence** is a term in pharmacokinetics used to assess **the expected *in vivo* biological equivalence** of two proprietary preparations of a drug.
- Bioequivalence studies are usually performed for **Generic Drugs**.

What are Generic Drugs?

- A common use of the term "**generic drug**" is for a pharmaceutical product that is:
  - intended to be interchangeable with the innovator product in an individual patient
  - usually manufactured without a license from the innovator company
  - marketed after expiry of patent or other exclusivity rights
- The WHO refers to these products as '**multisource pharmaceutical products**'.
- To be interchangeable such products must be **bioequivalent**.

Bioequivalence (BE)

- Two pharmaceutical products are **bioequivalent** if they are
  - **pharmaceutically equivalent**
  - and their **bioavailabilities** after administration in the same molar dose are **similar.**

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Pharmaceutical Equivalence

- Pharmaceutical equivalence implies
  - the **same amount** of the same active substance(s)
  - in the **same dosage form** (or pharmaceutical alternatives)
  - for the same route of administration
  - and meeting the same or comparable standards.

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Similar Bioavailability

- Similar bioavailabilty implies

  The **bioavailabilities** (rate and extent of availability) after administration in the **same molar dose** of the reference and test drug are **similar** to *such a degree that their effects, with respect to* both **efficacy and safety**, can be expected to be essentially the same.

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Generic versus Pioneer Product Equivalence Concepts (CFR 320)

- Pharmaceutical Equivalence
  - Same active ingredient
  - Same strength
  - Same dosage form and route of administration
  - Comparable labeling
  - Meet compendial or other standards of identity, strength, quality, purity and potency
- *Bioequivalence*
  - In vivo measurement of active moiety (moieties) in biologic fluid (blood/urine)
  - In vivo pharmacodynamic comparison
  - In vivo clinical comparison
  - In vitro comparison
  - Other
- THEN: THERAPEUTIC EQUIVALENCE

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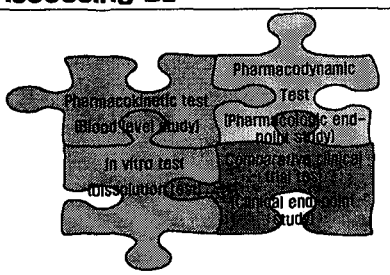
Assessing BE



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Bioavailability (BA)

- Bioavailability is a measurement of the **RATE** and **EXTENT** of a therapeutically active drug that reaches the systemic circulation and is available at the site of action.
- It is expressed as the letter *F*.

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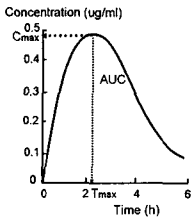
Guidelines and Regulation on BE Studies

Regulatory Definition (Foreign Countries)

- **US:** two products are bioequivalent
  - *if the 90% CI of the relative mean* **Cmax**, *AUC(0-t) and AUC(0-∞)* of the test (e.g. generic formulation) to reference (e.g. innovator brand formulation) are within **80.00%** to **125.00%** in the fasting state.
- **EU:** two medicinal products are bioequivalent
  - if they are pharmaceutically equivalent or pharmaceutical alternatives
  - and if their bioavailabilities after administration in the same molar dose are similar to such a degree that their effects, with respect to both efficacy and safety, will be essentially the same.
- **Australia:** two products are bioequivalent
  - if the 90% confidence intervals (90% CI) of the transformed natural log ratios, between the two preparations, of C_{max} and AUC lie in the range 0.80-1.25.
  - T_{max} should also be similar between the products.

Regulatory Definition (Korea)



➢비교평가항목 : AUC, Cmax
➢참고평가항목 : Tmax,
비교용출시험

➢대조약에 대한 시험약의 비교평가항목이 80 ~ 125% 이내일 때, 생물학적으로 동등하다고 판정!

Guidelines and Regulation (Korea)

- 생물학적동등성시험기준. 식품의약품안전청고시 제 2005-31호, 2005. 6. 7
- 생체시료분석법 Validation. 국립독성연구원, 2003. 5

- **→ GLP is not required.**

Guidelines and Regulation (Foreign)

- US FDA:
  - Code of Federal Regulation. Title 21, Part 320 - Bioavailability and bioequivalence requirements, FDA
  - Guidance for Industry-Bioavailability and Bioequivalence Studies for Orally Administered Drug Products –General Considerations
  - Guidance for Industry-Bioanalytical Method Validation
- EMEA: Note for Guidance on the Investigation of Bioavailability and bioequivalence. CPMP/EWP/QWP/1401/98. Japan: Guideline for Bioequivalence studies of Generic Products
- Canada: Drug Directorate guideline. Conduct and Analysis of Bioavailability and Bioequivalence Studies.

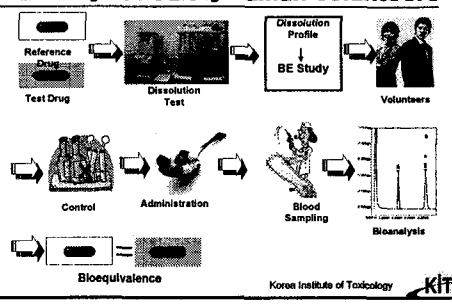
- **→ GLP is not required.**

Flow of Bioequivalence Studies

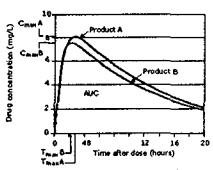
Assessing Bioequivalence

- Bioequivalence is usually assessed by single dose *in vivo* studies in healthy volunteers.
- The reference product is usually the innovator product that is marketed.

BE study in healthy human volunteers



Assessing BE



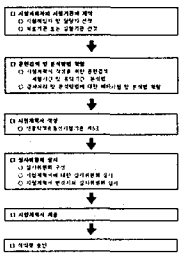
Drug A (reference drug): C_{max}=8.1 mg/L; T_{max}=2.6 h; AUC=124.9 mg·h/L

Drug B (generic drug): Cmax=8.1 mg/L; Tmax=2.6 h; AUC=124.9 mg·h/L

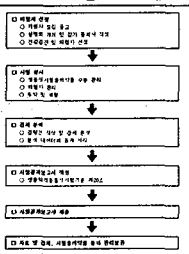
The ratio of areas (generic:reference) = 0.9

To be accepted as bioequivalent, the 90% intervals for the area raton would need to fall within the range 0.8-1.25

Flow of BE Study (Protocol)



Flow of BE Study (Report)



BE Study (KFDA)

생물학적동등성시험기준

- 심사위원회
  - 시험책임자 및 시험담당자 선임의 타당성 검토
  - 시험계획서의 타당성 검토 및 승인
  - 시험계획서의 중요사항 변경에 대한 승인
  - 피험자의 안전보호 및 보상 등 피험자 권익에 대한 타당성 검토
  - 피험자 선정 및 동의방법의 타당성 검토
  - 시험진행상황의 점검 및 시험 운영에 대한 의견 진술
  - 시험결과보고서 및 시험기초자료의 심사와 평가

BE Study (KFDA)

- 시험결과보고서
  1. 시험제목, 시험목적 및 시험결과의 요약
  2. 대조약 및 시험약의 성분명 및 함량, 제형, 제조일자, 제조번호, 품질관리시험성적서
  3. 시험약 제조에 사용한 원료의 제조자, 제조지, 공급자, 배치번호, 원료시험성적서 및 수입 원료의 경우 통관증명 등
  4. 시험약의 제조지시서
  5. 시험의뢰자의 성명 및 소속기관
  6. 시험기관의 명칭, 소재지, 시험기관장 성명
  7. 시험책임자 및 담당자의 성명, 소속 및 직책
  8. 시험기간
  9. 비교용출시험의 결과(제5조제1항제8호 단서 규정에 해당하는 경우는 제출하지 아니할 수 있다.)
  10. 예비시험 결과(사람을 대상으로 한 경우 피험자의 건강진단서, 동의서 등 피험자의 관리내역 포함)
  11. 피험자 선정기준 및 방법 : 피험자 선정 및 제외기준, 지원자 모집공고, 생물학적동등성시험 설명서, 피험자 동의서
  12. 외부기관에서 발행한 건강진단서(임상병리검사결과 및 건강소견 포함)
  13. 중도탈락자와 그 사유
  14. 증례기록서(채혈시간표 포함)
  15. 시험방법 : 투약량, 투약경로, 투약방법, 투약일, 검체채취방법, 채취량, 채취횟수 및 시간, 검체보관방법, 휴약기간
  16. 채혈인 경우 감염방지 대책
  17. 검체처리 및 분석방법 (validation자료 : 특이성, 직선성, 정확성, 정밀성, 감도 등)
  18. 시험결과 : 피험자별 각 채혈시간의 활성약물농도수치 등 분석실측치(디스켓 제출) 및 로그변환치, 분석결과 및 통계처리과정 (raw data) 포함
  19. 평가기준 및 시험결과에 대한 시험책임자의 종합의견
  20. 동물시험인 경우 동물의 종, 계통, 수, 연령, 성별, 체중, 공급원, 구입날짜 및 사육조건 등
  21. 심사위원회 기록서
  22. 생물학적동등성시험용 의약품 수불현황
  23. 심사위원회에서 최종 승인한 생물학적동등성시험 계획서

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GLP Perspectives in Bioequivalence Studies

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GLP in Nonclinical Studies

- ***Good Laboratory Practice (GLP)***: 의약품등의 안전성을 확인하기 위하여 이루어지는 비임상시험의 신뢰성을 확보하기 위한 기준으로, 시험기관의 조직, 시설 및 장비, 시험계획서 및 시험의 실시, 시험물질 및 대조물질, 시험의 운영, 보고 및 기록, 적격 시험기관 지정 및 감독 등 시험과정에 관련되는 모든 사항을 조직적으로 체계있게 관리할 수 있는 규정을 말함
- **GLP 규제의 발단:** 신약허가 검토를 받기위하여 제약기업이 규제당국에 제출하는 각종 시험자료는 정말로 적절하게 시험이 실시되었으며 또한 충분한 신빙성을 가지고 있는지를 알기 위해서 출발됨
- **GLP 규정의 목적:** 의약품, 의외품, 화장품등의 비임상적 안전성시험에 대한 제반 준수사항을 규정함으로써 시험과정 및 결과에 대한 신뢰성 확보를 목적으로 함

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GLP in Nonclinical Studies

- GLP Guideline (KFDA, OECD, FDA, EPA)
  - Scope and Authority
  - Definitions
  - Organization and Personnel
  - Facilities
  - Equipment
  - Facility Operation
  - Articles
  - Protocol and Conduct
  - Records and Reports
  - Disqualification

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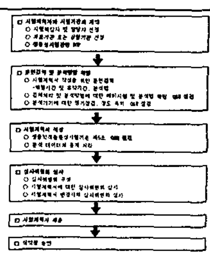
GLP Perspective of BE Study (Protocol)



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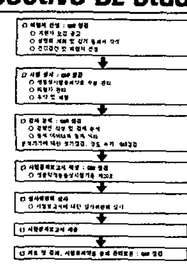
GLP Perspective BE Study (Report)



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Good Documentation Practice

- All data generated will be recorded directly, promptly, accurately, legibly and indelibly in permanent black ink.
- Error corrections
- Notebook: Include data expected to be recorded: title, purpose, materials, method, results, conclusion
- Supplemental binder: Include raw data and supporting data e.g., correspondence, sample tracking, deviation memos, QA statement etc.

Discussion

To Achieve Quality Assurance in BE Studies

- **BE Study under GLP Environment**
  - **Bioanalytical Method Validation**
  - **Protocol →→Dosing →→Sampling→→ Report**
  - **Sample Analysis**
- **QAU Involvement ?**
  - **Study-based inspections**
  - **Facility-based inspections**
  - **Process-based inspections**
- **Good Documentation Practice**
- **???**

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