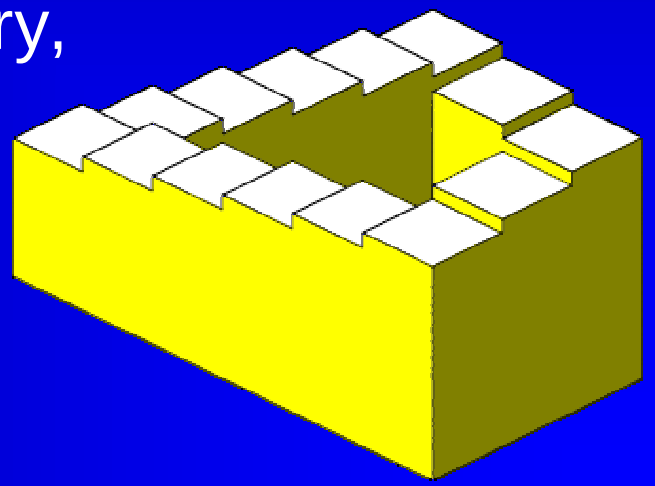
Considerations for planning and designing a bioequivalence (BE) study

Helmut Schütz
BEBAC
Consultancy Services for
Bioequivalence and Bioavailability Studies
1070 Vienna, Austria
helmut.schuetz@bebac.at

Main Topics

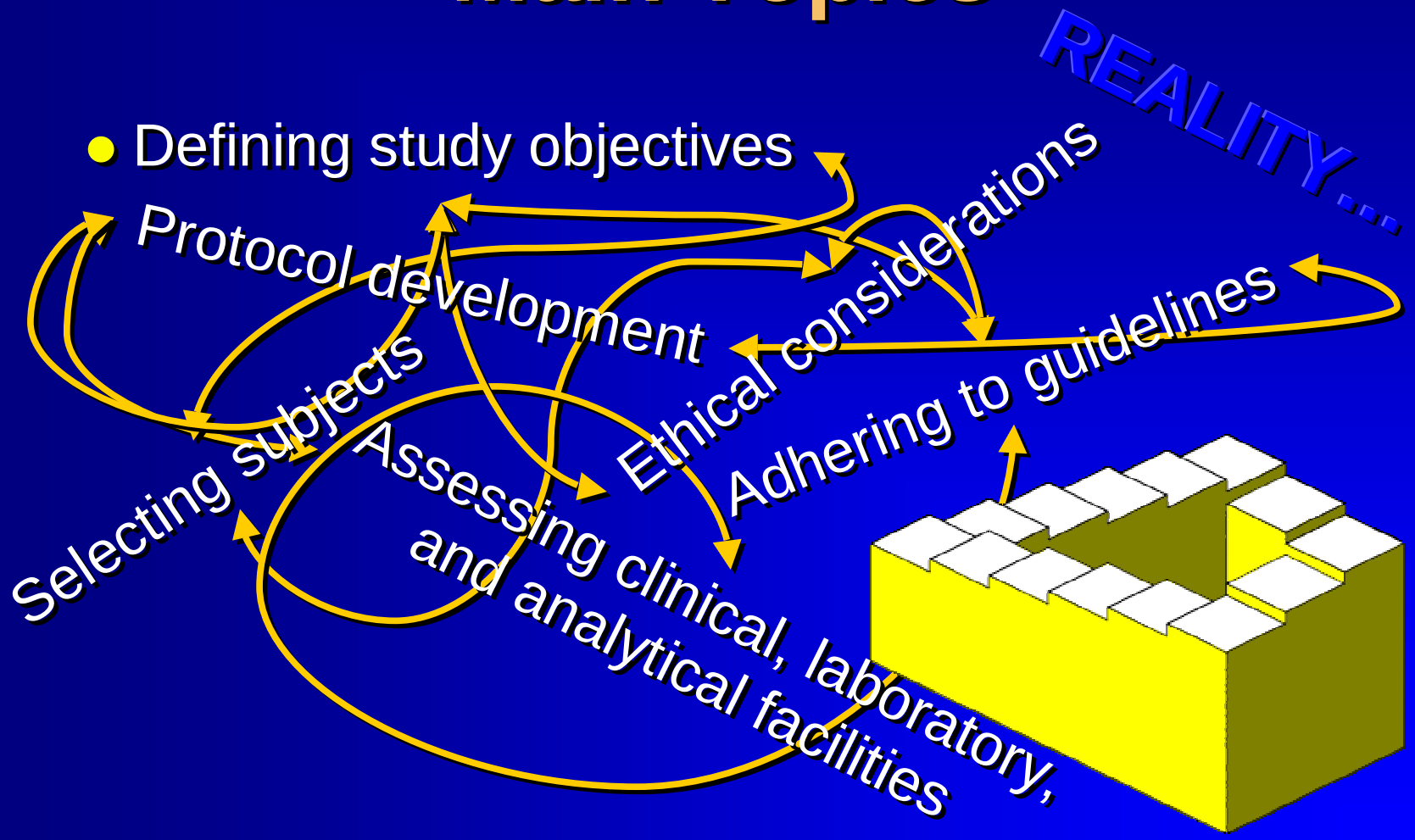
DREAM...

- Defining study objectives
- Protocol development
- Ethical considerations
- Assessing clinical, laboratory, and analytical facilities
- Selecting subjects
- Adhering to guidelines



Main Topics

- Defining study objectives



Defining study objectives

- According to the NfG (3. Design and Conduct of Studies, paragraph 2):

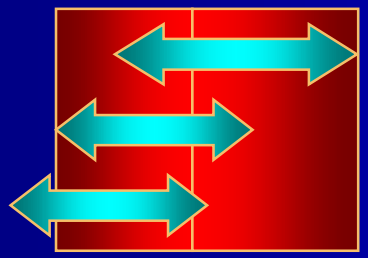
  'A bioequivalence study is basically a comparative bioavailability study designed to establish equivalence between test and reference products.'

  - Comparative BA,
  - designed to demonstrate BE,
  - reference = innovator's product.

EMEA Human Medicines Evaluation Unit / CPMP
Note for Guidance on the Investigation of Bioavailability and Bioequivalence
CPMP/EWP/QWP/1401/98 (26 July 2001)
http://www.emea.eu.int/pdfs/human/ewp/140198en.pdf#page=6

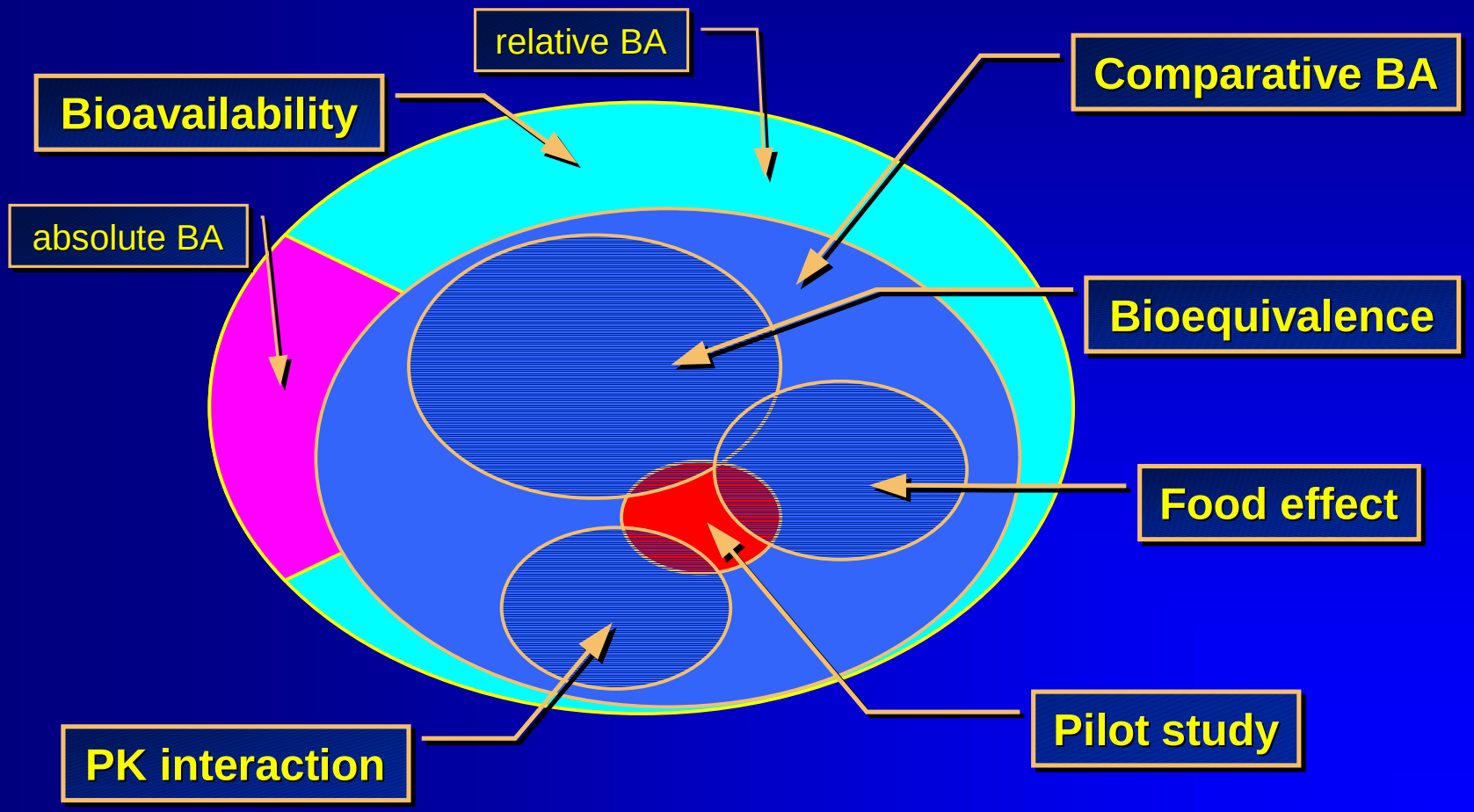
Defining study objectives

- Comparative BA
  - true experiment; no bibliographic comp.
- Designed to demonstrate BE
  - variability,
  - deviation of test from reference,
  - drop-out rate,…
  - ➔to be able (statistical power) to demonstrate BE
- Reference = innovator's product



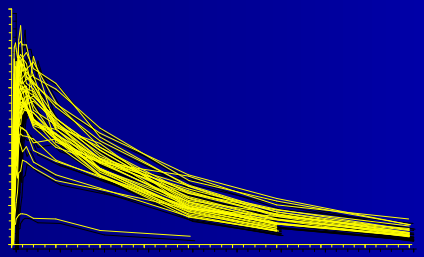
#1: BE [90%–125%]
#2: BE [80%–110%]
#3: not BE [76%–103%]; (but 'BE' to #2)

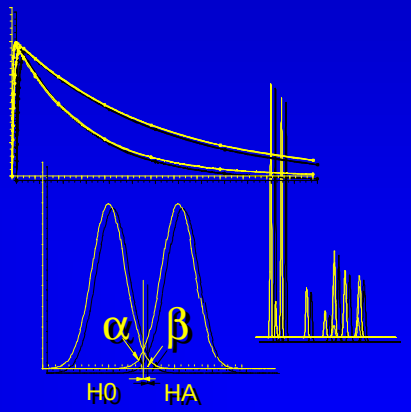
Terminology



Assumptions

World *'Reality'*





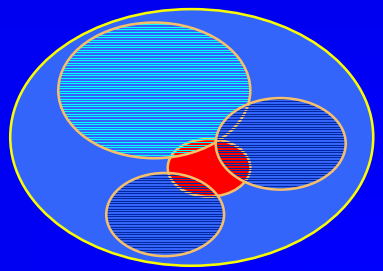
Model *'Data'*

Theory *'Truth'*

Defining study objectives

- Definition of BE (NfG, Section 2.4)

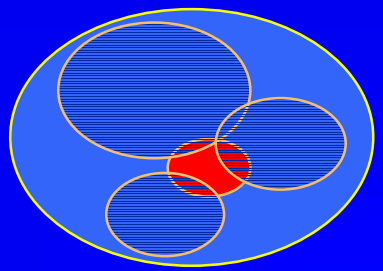
  'Two medicinal products are bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and if their bio-availabilities after administration in the same molar dose are similar to such degree that their effects, with respect to both efficacy and safety, will be essentially the same.'



Defining study objectives

- *In vivo* BE mandatory, if
  - Waiving (NfG Section 5.1.1) not possible
    - in MA of generics
    - Manufacturing changes (EU Major variation type II(d)-(f) ~ SUPAC Level 3)
  - Pharmacokinetic interaction studies,
  - Studies of fixed-combination products.

'[…] are similar to such degree that their effects, with respect to both efficacy and safety, will be essentially the same.'

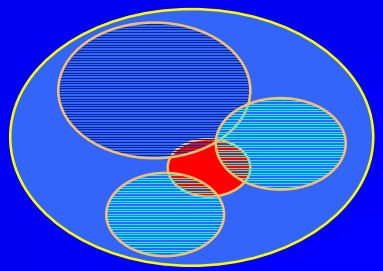


Defining study objectives

- Concept of BE also applicable to
  - Food effect studies,
  - Pharmacokinetic interaction studies,
  - Studies of fixed-combination products.

'[…] are similar to such degree that their effects, with respect to both efficacy and safety, will be essentially the same.'

EMEA Human Medicines Evaluation Unit / CPMP
Modified Release Oral and Transdermal Dosage Forms: Section II (Quality)
CPMP/EWP/280/96, London, 28 July 1999
EMEA Human Medicines Evaluation Unit / CPMP
The Investigation of Drug Interactions
CPMP/EWP/560/95, London, 17 December 1997
EMEA
Fixed Combination Medicinal Products
CPMP/EWP/240/95 Rev. 1, London, 21 February 2008



Protocol development

- Whatever procedure you do not lay down in the protocol likely will not be accepted by the competent authorities!
  - Clinical phase
    Requirements following the PK / safety profile of the API and organizational / economic constraints
    - Screening / post treatment (in-house *vs.* external)
    - Hospitalization *vs.* ambulatory
    - PD and/or safety parameters
    - Sampling / handling / storage / shipment

Protocol development

- Since *in vivo* BE relies on 'rich' PK data:
  - Sufficient number of blood samples (C_{max}!) / urine collection periods
  - Sampling long enough to cover ≥80 % of AUC_{∞}
  - Wash-out ≥3× $t_{½}$ (recomm. ≥5× $t_{½}$)
  - Saturation phase long enough to reach steady-state: ≥5× $t_{½}$ (recomm. ≥7× $t_{½}$)
  - Pre-dose samples (carry-over, compliance)

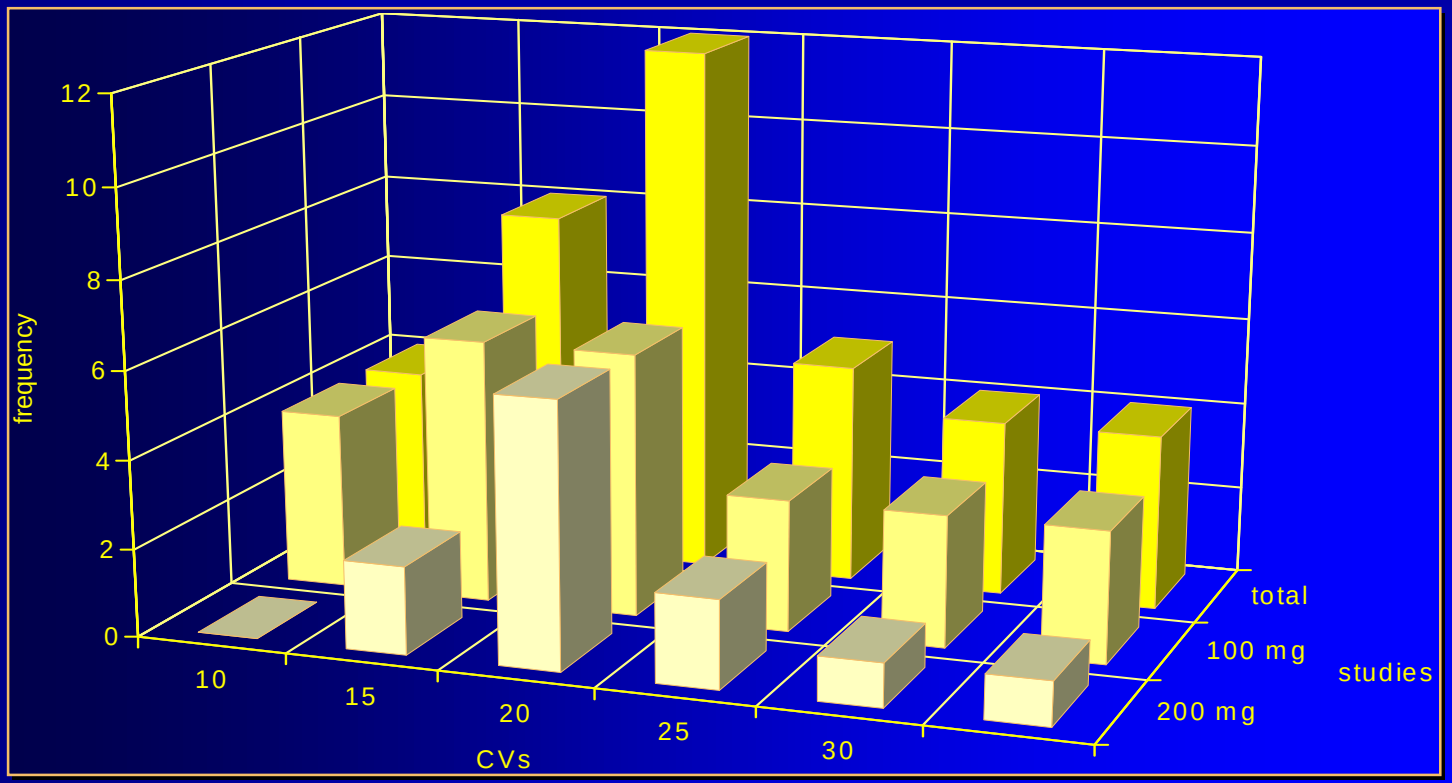
New NfG: for IR formulations no more sampling beyond 72 hours.

Protocol development

- Sample size planning (NfG, Section 3.1)
  - The number of subjects required is determined by
    - the error variance associated with the primary characteristic to be studied as estimated from
      - a pilot experiment,
      - previous studies, or
      - published data,
    - the significance level desired,
    - the expected deviation (Δ) from the reference product compatible with BE and,
    - the required power.

Protocol development

- Sample size planning



Doxicycline *(37 studies ref. by Blume/Mutschler, 1996)*

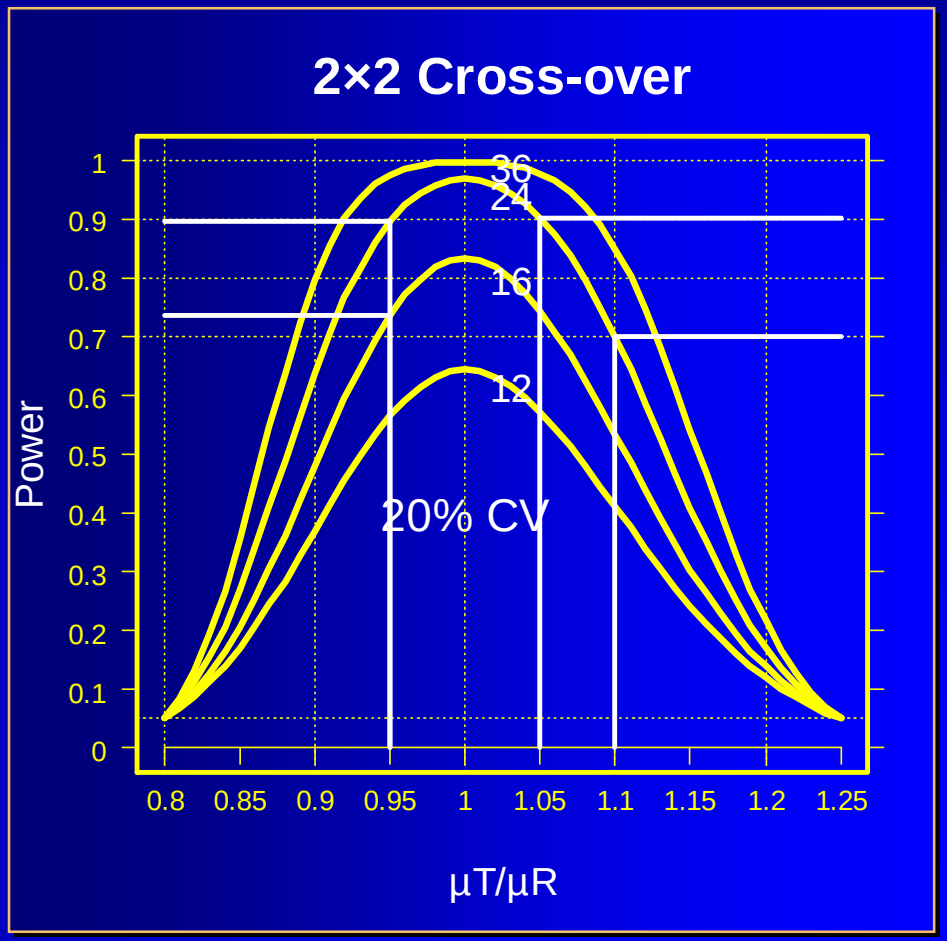
Protocol development

Power to show

BE with 12 – 36 subjects for CV_{intra} = 20%

n 24 → 16:
power 0.896 → 0.735

μT/μR 1.05 → 1.10:
power 0.903 → 0.700



Potency

- ANDAs approved by FDA/OGD 1996–2005 (1636 studies, 12–127 subjects)
  - with few exceptions: single dose, fasting
  - data referring to studies demonstrating BE on AUC_∞, AUC_t, C_{max}; deviation test/reference:
    - AUC_∞ 3.12% (±2.66%)
    - AUC_t 3.19% (±2.72%)
    - C_{max} 4.50% (±3.57%)

Nwakama PE, Haidar SH, Yang YS, Davit BM, Conner DP, Yu LX
Generic Drug Products Demonstrate Small Differences in Bioavailability Relative to the Brand Name Counterparts: A Review of ANDAs Approved 1996 – 2005
12th Annual FDA Science Forum, April 2006: Board A-18
http://www.accessdata.fda.gov/scripts/oc/scienceforum/sf2006/Search/preview.cfm?keyword=A&abstract_id=897&type=category&backto=search

Highly variable drugs

- All (!) ANDAs submitted to FDA/OGD 2003–2005 (1010 studies, 180 drugs)
  - 31% (57/180) highly variable (CV ≥30%)
  - of these HVDs/HVDPs,
    - 60% due to PK (*e.g.*, first pass metabol.)
    - 20% formulation performance
    - 20% unclear

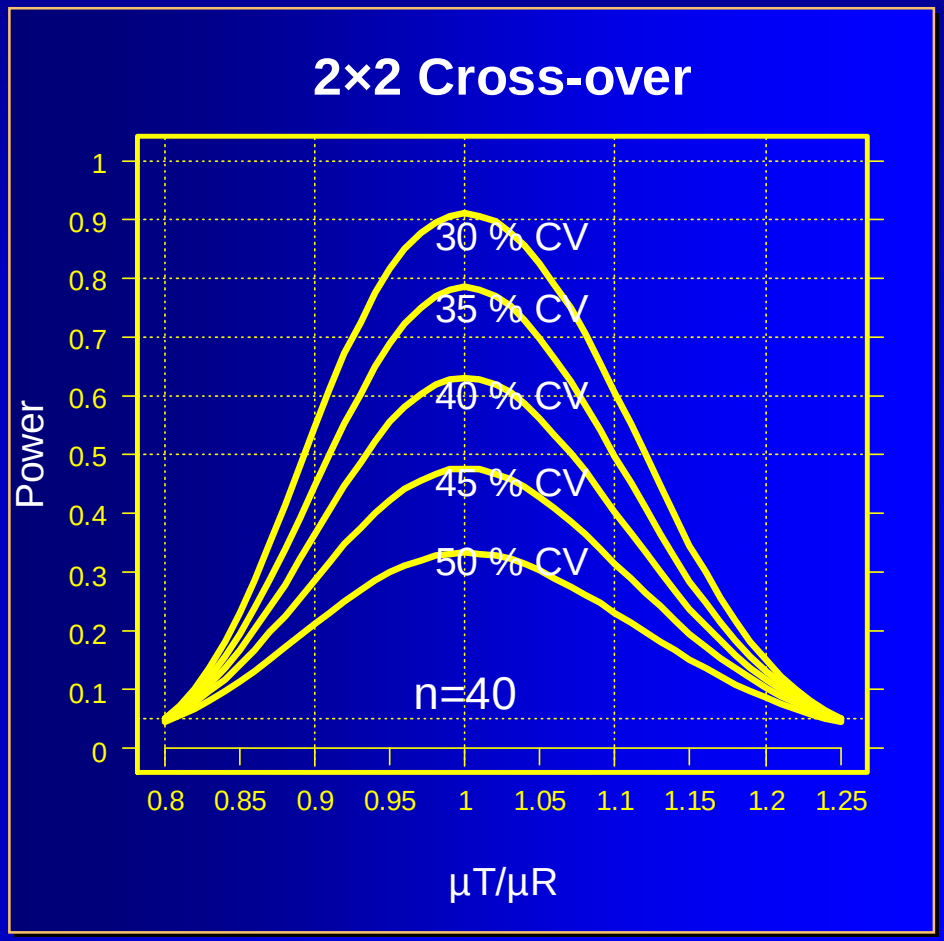
Davit BM, Conner DP, Fabian-Fritsch B, Haidar SH, Jiang X, Patel DT, Seo PR, Suh K, Thompson CL, Yu LX
Highly variable drugs: observations from bioequivalence data submitted to the FDA for new generic drug applications
AAPS J 10(1): 148-56 (2008)

HVDs

Power to show BE with 40 subjects for CV_{intra} = 30–50%

$\mu T/\mu R$ 0.95, CV_{intra} 30%
→ power 0.816
$\mu T/\mu R$ 1.00, CV_{intra} 45%
→ power 0.476 <
Roulette 0.486 (!)

$\mu T/\mu R$ 0.95, CV_{intra} 45%
→ n=82 (power 0.807)



HVDs (US/EU)

- Advisory Committee for Pharmaceutical Sciences (ACPS) to FDA (10/2006) on HVDs
- Follow-up paper in 2008 (likely to be implemented in next Guideline)
  - Replicate study design [TRR–RTR–RRT]
  - Reference Scaled Average Bioequivalence (RSABE)
  - Minimum sample size 24 subjects
  - Point estimate restricted to [0.80,1.25]

SH Haidar, B Davit, M-L Chen, D Conner, LM Lee, QH Li, R Lionberger, F Makhlouf, D Patel, DJ Schuirmann, and LX Yu
Bioequivalence Approaches for Highly Variable Drugs and Drug Products
Pharmaceutical Research 25/1, 237-241 (2008)
http://www.springerlink.com/content/u503p62056413677/fulltext.pdf

HVDs (EU)

- Questions & Answers document (July 2006)
  - #2: referring to the NfG:

    "*In certain cases a wider interval […] prospectively defined, e.g. 0.75 – 1.33, and justified addressing in particular any safety or efficacy concerns for patients switched between formulations".*
  - Widening only for C_{max} (not for AUC)
    - exceptional, and
    - limited to a small widening (0.75 − 1.33).

HVDs (EU)

- Q & A document (cont.'d)
  - Widening for C_{max}
    - Restricted to products for which at least one of the following criteria applies:
      1) Data on PK/PD relationships (safety and efficacy) adequate to demonstrate that PD is not affected in a clinically significant way.
      2) If PK/PD data are inconclusive or not available, clinical safety and efficacy data may be used, but specific for the compound and persuasive.
      3) Reference product is a HVDP. See #8 of the Q&A document.

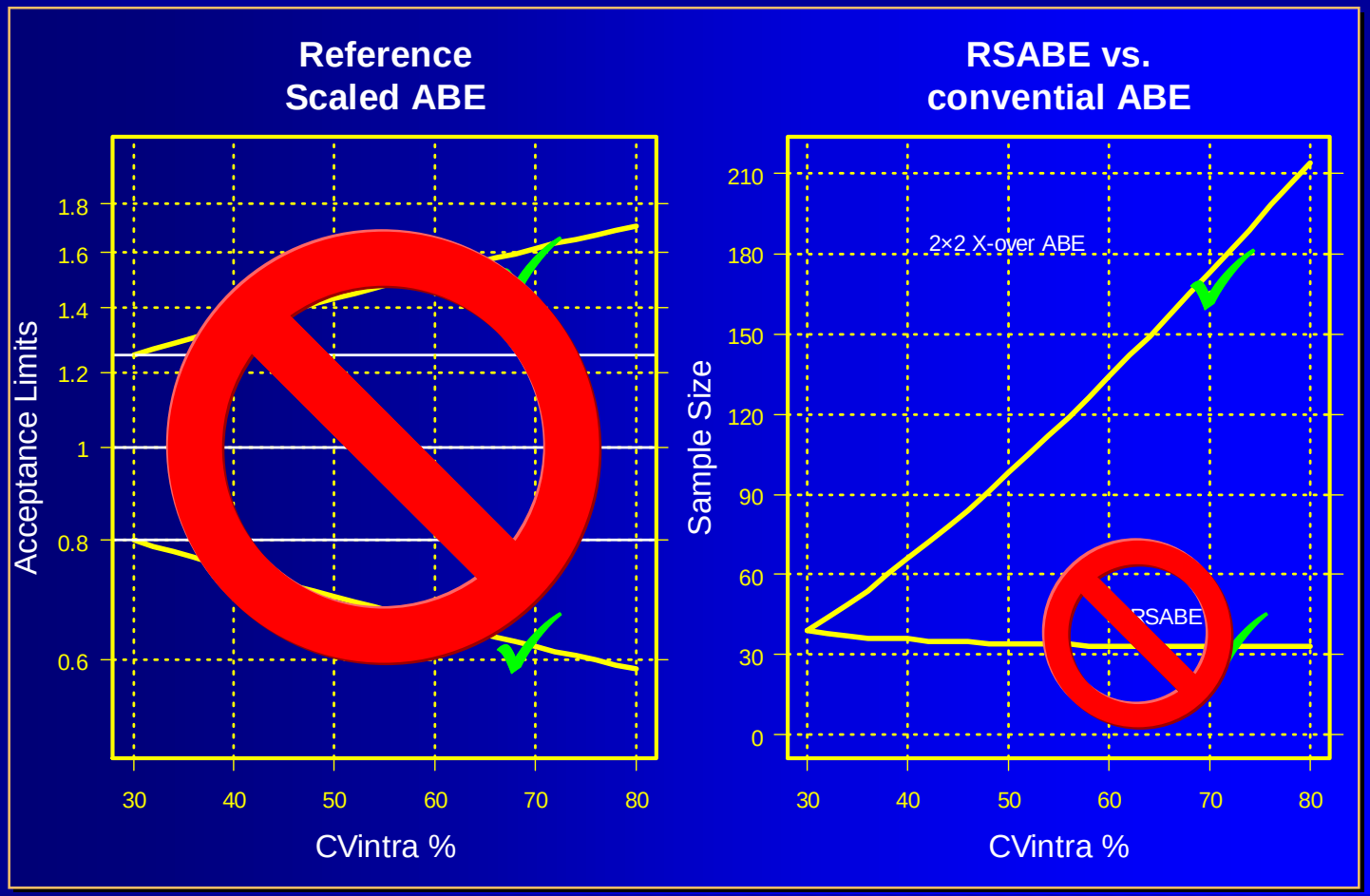
    Different interpretation of both the NfG and the Q&A document within the European Union.*)

*) **European Generic Medicines Association**
1st EGA Workshop on Bioequivalence Study Design, Working to GCP and Interpreting the Guidelines
Lisbon, October 23rd-24th, 2007

HVDs (EU)

- Q & A document (cont.'d)
  - #8: Demonstration of HVDP calls for a replicate design pilot study (literature data and/or intra-subject CV from a 2×2 cross-over study not accepted).
    - Recommended replicate design:
      3 period 2 sequence [TRT–RTR]

HVDs (US/EU)


Reference
Scaled ABE
Acceptance Limits
1.8
1.6
1.4
1.2
1
0.8
0.6
30
40
50
60
70
80
CVintra %
RSABE vs.
convential ABE
Sample Size
210
180
150
120
90
60
30
0
2×2 X-over ABE
RSABE
30
40
50
60
70
80
CVintra %

Protocol development

- Analytical part; NfG (Section 3.4)
  - *[…] should be conducted according to the applicable principles of Good Laboratory Practice (GLP).*
    - Six characteristics
      - Stability of the stock solutions and of the analyte(s) in the biological matrix under processing conditions and during the entire period of storage
      - Specificity
      - Accuracy
      - Precision
      - Limit of quantification
      - Response function

Protocol development

- Analytical part; NfG (Section 3.4)
  - Prestudy phase: verification of the compliance of the assay with the six characteristics
  - Study phase: application af the validated bioanalytical method to analysis of samples from the biostudy
    - Calibration per batch / set of QC samples
    - Stability
    - Accuracy
    - Precision

U.S. Department of Health and Human Services, FDA/CDER/CVM
Guidance for Industry: Bioanalytical Method Validation, May 2001 http://www.fda.gov/cder/guidance/4252fnl.pdf

Viswanathan, CT, *et al.*
Workshop/Conference Report—Quantitative Bioanalytical Methods Validation and Implementation: Best Practices for Chromatographic and Ligand Binding Assays
The AAPS Journal 9(1) Article 4, E30-E41, 2007
http://www.aapsj.org/articles/aapsj0901/aapsj0901004/aapsj0901004.pdf

Ethical considerations

- Cross-over design not always feasible
  - Long half live drugs
  - Patients: changes in disease state
  - Safety considerations
- Healthy subjects *vs.* patients
  - Healthy subjects generally preferred, except
    - Main effect or adverse reactions unacceptable (antipsychotics, chemotherapeutic agents, …)
  - Hormones in postmenopausal women (analytics)

Ethical considerations

- Polymorphism
  - Phenotyping
    - In all parallel design studies (fast metabolizers only)
    - Safety: in steady-state studies (fast metabolizers only; example: paroxetine)
  - Genotyping?
    - Pro: no additional administration of a ‘model drug’.
    - Con: very restrictive (informed consent, data protection, …) in some countries.

Selecting subjects

- NfG (Section 3.2)

  'The subject population for bioequivalence studies should be selected with the aim to minimise variability and permit detection of differences between pharmaceutical products. Therefore, the studies should normally be performed with healthy volunteers. The inclusion/exclusion criteria should be clearly stated in the protocol.'

Selecting subjects

- NfG (Section 3.2 cont.'d)

  '… performed with healthy volunteers. ♂♀; however, the risk to women of childbearing potential should be considered on an individual basis.' (acc. to ICH, but BfArM …)

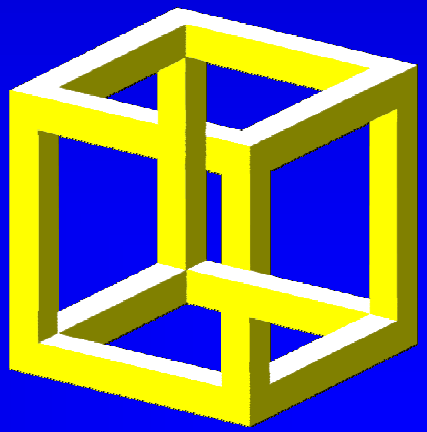
  '… preferably […] non-smokers […]. If moderate smokers are included (<10 cigarettes / day) they should be identified as such and the consequences for the study results should be discussed.'

EMEA
Gender Considerations in the Conduct of Clinical Trials
EMEA/CHMP/3916/2005 – ICH, London 2005-01-05
http://www.emea.europa.eu/pdfs/human/ich/391605en.pdf

Is the API metabolized by cytochrome P450 1A1?

In-house *vs.* outsourcing

- Assessing clinical, laboratory, and analytical facilities
  - Accoding to ICH-EG (GCP) and 2001/20/EC the responsibility resides with the sponsor
  - Bigger *not necessarily* = better
  - Pre-study vendor/facility audit mandatory
  - Search external expertise – or even better – develop your own



Adhering to guidelines

- NfG (Section 2.4, paragraph 2)

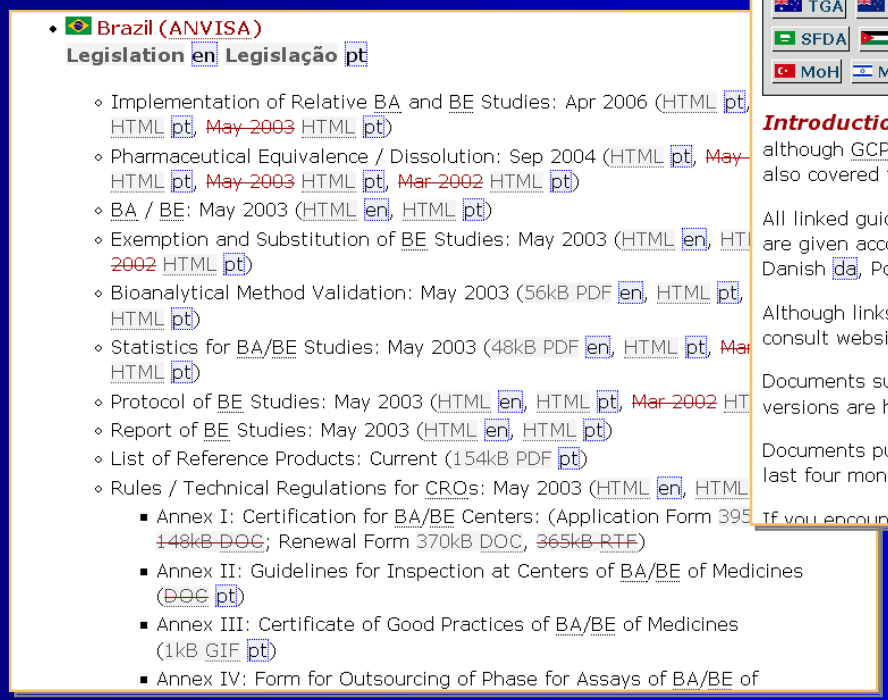
  'Alternatively […], other types of studies can be envisaged, e.g. human studies with clinical or pharmacodynamic end points, studies using animal models or in vitro studies as long as they are appropriately justified and/or validated.'

  - Sure, but…
  - Be prepared for the unforessen!

EMEA Inspectors Working Group
Advice to Applicants/Sponsors/CROs of BE Studies
EMEA/INS/GCP/468975/2007, London, 18 October 2007
http://www.emea.europa.eu/Inspections/docs/46897507en.pdf

Adhering to guidelines

- Guideline Collection
  http://bebac.at/Guidelines.htm



- Brazil (ANVISA)
  Legislation en **Legislação** pt
  - Implementation of Relative BA and BE Studies: Apr 2006 (HTML pt, HTML pt, ~~May 2003~~ HTML pt)
  - Pharmaceutical Equivalence / Dissolution: Sep 2004 (HTML pt, ~~May~~ HTML pt, ~~May 2003~~ HTML pt, ~~Mar 2002~~ HTML pt)
  - BA / BE: May 2003 (HTML en, HTML pt)
  - Exemption and Substitution of BE Studies: May 2003 (HTML en, HT ~~2002~~ HTML pt)
  - Bioanalytical Method Validation: May 2003 (56kB PDF en, HTML pt, HTML pt)
  - Statistics for BA/BE Studies: May 2003 (48kB PDF en, HTML pt, ~~Mar~~ HTML pt)
  - Protocol of BE Studies: May 2003 (HTML en, HTML pt, ~~Mar 2002~~ HT
  - Report of BE Studies: May 2003 (HTML en, HTML pt)
  - List of Reference Products: Current (154kB PDF pt)
  - Rules / Technical Regulations for CROs: May 2003 (HTML en, HTML
    - Annex I: Certification for BA/BE Centers: (Application Form 395 ~~148kB DOC~~; Renewal Form 370kB DOC, ~~365kB RTF~~)
    - Annex II: Guidelines for Inspection at Centers of BA/BE of Medicines (~~DOC~~ pt)
    - Annex III: Certificate of Good Practices of BA/BE of Medicines (1kB GIF pt)
    - Annex IV: Form for Outsourcing of Phase for Assays of BA/BE of

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Guidelines & Guidance Documents

ICH | WHO | EMEA | DKMA | MEB | FDA | HPFB | NIHS | MCC
TGA | Medsafe | CDSCO | PAHO | ANVISA | Secr. de Salud | ANMAT
SFDA | MoH | ACCSQ | BPFK | FDA | HSA | KFDA | CDE | Swissmedic
MoH | MoH | OECD

Introduction Main topic of this collection is Bioavailability / (*in-vivo*-) Bioequivalence, although GCP/GLP, dissolution/BCS, pharmacokinetics, bioanalytics and -statistics are also covered to some minor extent.

All linked guidances/guidelines are in English, unless stated otherwise. Language codes are given according to ISO 639-1 (*i.e.*, English en, French fr, German de, Spanish es, Danish da, Portuguese pt, Japanese ja, Chinese zh, Arabic ar,...)

Although links to documents are considered current with 08 June 2008, you should always consult websites of the respective regulatory body for any updated versions.

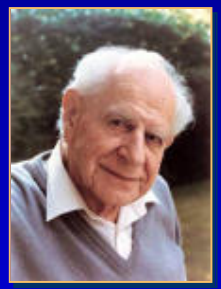
Documents superseded by newer versions are ~~striken through~~. While obsolete, previous versions are helpful in dealing with deficiency letters issued for older studies.

Documents published within the last two years are marked. Updates and additions in the last four months: →1, →2, →3, →4, →5.

If you encounter broken links or are acquainted with any missing / updated documents

To bear in remembrance...

Whenever a theory appears to you as the only possible one, take this as a sign that you have neither understood the theory nor the problem which it was intended to solve.

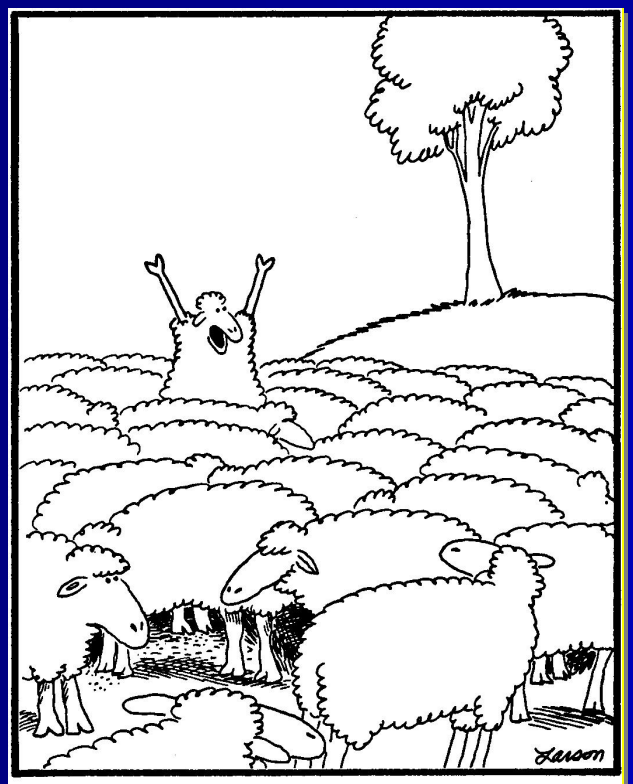


Karl R. Popper

Even though it's *applied* science we're dealin' with, it still is – *science!*

Leslie Z. Benet

Conclusions, Outlook



**“Wait! Wait! Listen to me! …
We don’t HAVE to be just sheep!”**

- David Bourne’s (Uni. Oklahoma) e-mail list
  - A rather active list (3200+ members, about 50 postings/week) covering almost any aspect of PK/PD/bio-analytics…
    - Subscription http://www.boomer.org/pkin/
    - Search page http://www.boomer.org/pkin/simple.html
- BA and BE Forum (BEBAC Vienna)
  - Specialized in BA/BE/bioanalytics.
    - No registration necessary to *read* posts. http://forum.bebac.at/
    - Registration (to post): http://forum.bebac.at/register.php

Ready for planning and designing a bioequivalence (BE) study?

Thank You!

Helmut Schütz
BEBAC
Consultancy Services for
Bioequivalence and Bioavailability Studies
1070 Vienna, Austria
helmut.schuetz@bebac.at

References

EMEA Human Medicines Evaluation Unit / CPMP

NfG on the Investigation of Bioavailability and Bioequivalence
CPMP/EWP/QWP/1401/98, 2001-07-26
http://www.emea.eu.int/pdfs/human/ewp/140198en.pdf

Questions & Answers on the BA and BE Guideline
EMEA/CHMP/EWP/40326/2006, 2006-07-26
http://www.emea.europa.eu/pdfs/human/ewp/4032606en.pdf

Modified Release Oral and Transdermal Dosage Forms: Section II (Quality)
CPMP/EWP/280/96, 1999-07-28
http://www.emea.europa.eu/pdfs/human/ewp/028096en.pdf

The Investigation of Drug Interactions
CPMP/EWP/560/95, 1997-12-17
http://www.emea.europa.eu/pdfs/human/ewp/056095en.pdf

Fixed Combination Medicinal Products
CPMP/EWP/240/95 Rev. 1 2008-02-21
http://www.emea.europa.eu/pdfs/human/ewp/024095en.pdf

Recommendation on the Need for Revision of NfG on BA/BE
EMEA/CHMP/EWP/200943/2007, 2007-05-24
http://www.emea.europa.eu/pdfs/human/ewp/20094307en.pdf

EMEA Inspectors Working Group

Advice to Applicants/Sponsors/CROs of BE Studies
EMEA/INS/GCP/468975/2007, 2007-10-18
http://www.emea.europa.eu/Inspections/docs/46897507en.pdf

The European Parliament and the Council of the European Union; Directives

2001/20/EC (Implementation of GCP in the Conduct of Clinical Trials on Medicinal Products for Human Use): 2001-04-04
http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/dir_2001_20/dir_2001_20_en.pdf

2003/94/EC (Principles and Guidelines of GMP in Re-spect of Medicinal Products for Human Use and Investi-gational Medicinal Products for Human Use): 2003-10-08
http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/dir_2003_94/dir_2003_94_en.pdf

2004/9/EC (Inspection / Verification of GLP): 2004-02-11
http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:050:0028:0043:EN:PDF

2005/28/EC (Principles and detailed Guidelines for GCP as regards IMPs for Human Use, as well as the Require-ments for Authorisation of the Manufacturing or Importa-tion of such Products): 2005-04-08
http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/dir_2005_28/dir_2005_28_en.pdf