Investigation of highly variable drugs in a patient population

Replicate design studies and differing requirements in EU and US

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Agenda

- **General aspects / introduction**
- **Highly variable drugs / replicate study design**
- **General aspects and examples for studies in patients**

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Bioequivalence guideline from EMA

- BE studies are normally done in healthy volunteers. A single dose cross-over design is recommended.
- If the drug is known to have adverse effects, and the pharmacological effects or risks are considered unacceptable for healthy volunteers, inclusion of patients may be necessary.
- Conduct of multiple dose study in patients is acceptable if a single dose study cannot be conducted in healthy volunteers due to tolerability reasons, and a single dose study is not feasible in patients.
- In steady-state studies, the wash-out period can overlap with the build-up of the second treatment, provided the build-up period is sufficiently long ($\geq 5 \times t_{1/2}$).

→ patients in case of safety issues

→ single dose or steady-state

Bioequivalence guideline from FDA

- This guidance recommends that in vivo BE studies be conducted in individuals representative of the general population, taking into account age, sex and race.

- In some cases, it might be useful to admit patients into BE studies for whom a drug product is intended. In this case disease process should be stable for the duration of the BE study.

→ patients possible in case disease is stable

BE studies in special patient populations

Examples mentioned in FDA guidances:

Drug substance	Indication group
Altretamine, Azacitidine, Capecitabine, Doxorubicine, Everolimus, Goserelin, Hydroxyurea, Imatinib, Methotrexate, Cyclophosphamide, Mercaptopurine, Nabilone, Sunitinib, Vorinostat	Chemotherapeutics, Cytostatics
Azathioprine	Immunosuppressive drug
Clozapine	Antipsychotic drug
Felbamate	Anticonvulsive drug
Ganciclovir	Antiviral drug
Mebendazol	Anthelmintic drug
Testosterone	Sex hormone

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Highly variable drugs (HVDs)

Definition:

Within-subject variability > 30 %
HVDs generally have a wide therapeutic window as they are safe and effective despite the high variability.

Impact on sample size:

Due to the high variability more subjects are needed to reach the bioequivalence (BE) limits of 80 -125% in case of HVDs.

e.g. T/R ratio ± 5%, power 80%:

CV = 20 % → n=19 *
CV = 40 % → n=66 *

Conclusion:

As HVDs have a wide therapeutic window and the number of required subjects should be feasible, a widening of acceptance limits based on reference variability was implemented by authorities (reference-based scaling approach).

* according to Diletti, 1991

Highly variable drug approach

FDA	
before 2010	Many lectures on FDA conferences and published articles on BE approach for HVDs.
April 2010	Reference-scaled average bioequivalence approach published. Method for statistical analysis described in the draft guidance on progesterone.

EMA	
before August 2010	BE guideline (CPMP/EWP/QWP/1401/98, 2001): wider acceptance limits e.g. 75-133% may be acceptable for C_{max} if based on a sound clinical justification
after August 2010	Updated BE guideline (CPMP/EWP/QWP/1401/98, 2001,Rev.1, 2010): wider acceptance limits for C_{max} will be calculated using reference-scaled average bioequivalence approach

Replicate study design

Replicate designs may offer several advantages compared to non-replicate designs:

- design of choice for HVDs or borderline within-subject variability
  → increase chances for BE assessment
- reduced number of subjects required for BE study
  → reduction in recruitment period and costs
  → option for studies in patients
- both EMA and FDA developed this approach for HVDs to reduce the regulatory burden

	semi replicate	full replicate
design	TRR	TTRR
intra-CV	only reference	reference + test
		higher drop-out rate longer duration

Reference-scaled BE approach: Comparison of US and EU

	US	EU
basic approach	scaled average BE (SABE)	average BE with expanding limits (ABEL)
method applicable if	Intra-CV > 30 % = S_{WR} > 0.294	Intra-CV > 30 % = S_{WR} > 0.294
within-subject variability (S_W)	based on reference only	based on reference only
Applicable for	AUC and Cmax	only Cmax
Differences: regulatory constant (k) regulatory limit ($б_O$)	k = 0.893 $б_O$ = 0.25	k = 0.76 $б_O$ = 0.294
Formula	$\left(\bar{Y}_T - \bar{Y}_R\right)^2 - \theta s_{WR}^2$	$[U, L] = \exp[\pm k \cdot s_{WR}]$
Acceptance criteria		
T/R ratio of geomean should be within	80.00 - 125.00 %	80.00 – 125.00 %
BE assessment based on	95% upper confidence bound ≤0	90 % confidence limits within the given range

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Reference-scaled BE approach: Comparison of US and EU

	US	EU
no further widening of limits if intra-CV ≥ 50%	n.a.	yes maximum 69.84 – 143.19 %
pre-specification in protocol	✓	✓
clinical justification of wider acceptance limits	n.a.	✓
high CV not caused by outliers	n.a.	✓

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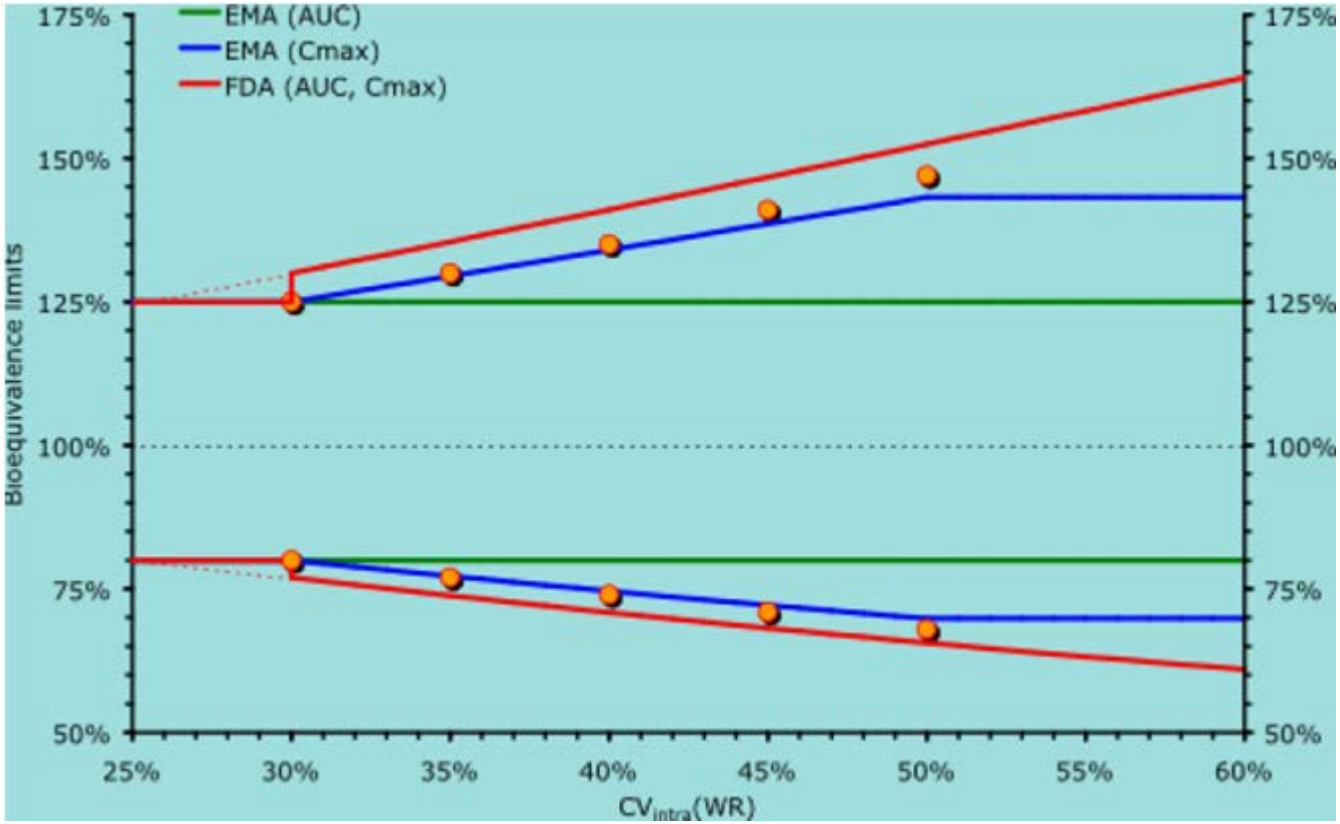
Reference-scaled BE approach: Comparison of US and EU

Acceptance ranges for Reference-Based Scaling:



Source: http://forum.bebac.at/mix_entry.php?id=6111#p6116, 27 Jan 2011

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Replicate study design: Sample size tables for EU studies

Within-subject CV (%)	Lower Limit	Upper Limit
30	80.00	125.00
35	77.23	129.48
40	74.62	134.02
45	72.15	138.59
≥50	69.84	143.19

Ref.: BE Guideline, CPMP/EWP/QWP/1401/98 Rev. 1, 2010

Table A1. Sample sizes for the requirements of EMA in 3-period studies

		80% POWER							
CV	GMR	0.85	0.90	0.95	1.00	1.05	1.10	1.15	1.20
30%		194	53	27	22	26	45	104	>201
35%		127	51	29	25	29	45	84	>201
40%		90	44	29	27	30	42	68	139
45%		77	40	29	27	29	37	57	124
50%		75	40	30	28	30	37	53	133
55%		81	42	32	30	32	40	56	172
60%		88	46	36	33	36	44	63	>201
65%		99	53	40	37	40	50	71	>201
70%		109	58	45	41	45	56	80	>201
75%		136	67	50	46	50	62	89	>201
80%		144	72	54	51	55	68	97	>201

		90% POWER							
CV	GMR	0.85	0.90	0.95	1.00	1.05	1.10	1.15	1.20
30%		>201	74	36	28	36	62	147	>201
35%		181	70	39	32	39	63	117	>201
40%		130	61	38	33	39	57	94	>201
45%		132	55	37	33	38	51	85	>201
50%		158	55	39	34	38	51	84	>201
55%		178	59	41	37	41	53	97	>201
60%		199	64	45	41	46	60	112	>201
65%		>201	72	51	46	51	67	125	>201
70%		>201	82	57	52	57	76	141	>201
75%		>201	93	66	58	64	85	161	>201
80%		>201	100	70	63	71	93	176	>201

CV: Coefficient of variation; GMR: Ratio of geometric means

Table A2. Sample sizes for the requirements of EMA in 4-period studies

		80% POWER							
CV	GMR	0.85	0.90	0.95	1.00	1.05	1.10	1.15	1.20
30%		127	35	19	15	18	30	68	>201
35%		88	34	20	18	20	31	57	140
40%		64	31	20	18	20	28	47	98
45%		57	29	21	19	21	27	41	90
50%		54	28	22	20	21	27	38	100
55%		55	30	23	21	23	28	40	116
60%		60	32	25	23	25	31	44	124
65%		74	37	28	26	28	33	49	155
70%		78	40	31	28	31	38	55	167
75%		85	45	34	32	34	42	61	186
80%		95	50	38	35	37	46	66	>201

		90% POWER							
CV	GMR	0.85	0.90	0.95	1.00	1.05	1.10	1.15	1.20
30%		180	49	25	19	24	42	95	>201
35%		123	48	27	22	27	43	80	>201
40%		93	42	26	23	26	39	66	165
45%		90	40	27	24	27	37	59	181
50%		102	39	27	25	27	36	60	>201
55%		123	41	29	26	29	38	63	>201
60%		139	45	32	29	31	41	71	>201
65%		159	51	36	32	35	46	81	>201
70%		172	55	40	36	40	52	97	>201
75%		195	62	43	39	44	58	106	>201
80%		>201	69	49	45	49	62	113	>201

CV: Coefficient of variation; GMR: Ratio of geometric means

Ref.: Tothfalusi, J. Pharm.Pharmaceutic Sci. 15 (1) 73-84, 2012

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Replicate study design: Sample size tables for US studies

Table A3. Sample sizes for the requirements of FDA in 3-period studies

CV	GMR	0.85	0.90	0.95	1.00	1.05	1.10	1.15	1.20
	80% POWER								
30%		145	45	24	21	24	39	82	>201
35%		74	37	24	22	25	34	54	109
40%		60	33	24	22	24	31	47	104
45%		59	31	23	22	24	29	43	116
50%		66	30	24	22	23	28	41	133
55%		80	30	24	22	24	28	44	172
60%		88	31	24	23	24	30	50	>201
65%		98	32	25	24	25	31	53	>201
70%		106	35	26	25	26	31	62	>201
75%		136	38	27	26	27	34	70	>201
80%		144	40	29	27	29	37	76	>201
	90% POWER								
30%		>201	65	33	26	32	55	122	>201
35%		106	51	32	28	32	47	77	186
40%		99	45	31	28	31	43	68	>201
45%		128	43	30	28	30	40	69	>201
50%		158	45	31	28	30	40	79	>201
55%		178	50	31	28	31	42	96	>201
60%		199	54	33	30	34	50	112	>201
65%		>201	61	35	32	36	53	125	>201
70%		>201	68	39	34	37	61	141	>201
75%		>201	80	43	37	41	68	161	>201
80%		>201	83	48	41	47	75	176	>201

CV: Coefficient of variation; GMR: Ratio of geometric means

Table A4. Sample sizes for the requirements of FDA in 4-period studies

CV	GMR	0.85	0.90	0.95	1.00	1.05	1.10	1.15	1.20
	80% POWER								
30%		96	30	17	15	17	27	55	200
35%		54	26	18	16	18	24	39	79
40%		43	24	18	16	17	22	33	72
45%		44	23	18	16	17	21	32	82
50%		45	22	17	17	17	21	31	99
55%		52	22	18	17	17	21	31	116
60%		58	23	18	17	18	21	34	124
65%		74	24	19	18	18	22	36	155
70%		75	24	19	18	19	23	44	167
75%		81	26	20	19	20	24	47	186
80%		95	29	21	20	20	25	51	>201
	90% POWER								
30%		152	44	23	18	22	38	81	>201
35%		80	38	23	20	23	34	55	128
40%		70	32	22	20	22	30	48	158
45%		84	32	22	20	22	30	49	181
50%		102	32	23	20	22	30	54	>201
55%		123	34	23	21	22	31	61	>201
60%		139	38	24	22	24	33	71	>201
65%		159	44	26	23	25	35	81	>201
70%		172	46	26	24	27	43	97	>201
75%		195	53	29	26	29	48	106	>201
80%		>201	60	33	28	31	51	113	>201

CV: Coefficient of variation; GMR: Ratio of geometric means

Ref.: Tothfalusi, J. Pharm.Pharmaceutic Sci. 15 (1) 73-84, 2012

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Reference-scaled BE approach: Comparison of US and EU

80% power *					
		semi-replicate		full-replicate	
CV	Ratio	US	EU	US	EU
30%	90%	45	53	30	35
35%	90%	37	51	26	34
50%	90%	30	40	22	28
60%	90%	31	46	23	32

→ lower sample sizes needed for US studies due to calculation difference

→ scaling possible for AUC and Cmax only in US

* Ref.: Tothfalusi, J. Pharm.Pharmaceutic Sci. 15 (1) 73-84, 2012

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General aspects for studies in patient populations

Study population

- detailed / special inclusion and exclusion criteria
- type of cancer, state/activity of disease
  → homogenicity of study collective

Treatment

- mono or in combination, in treatment cycles or continuous
- standard or individualized dose
  - stable dose over the whole study *
  - dose normalization in PK analysis
  - dose included as co-variable in ANOVA *
- co-medication → selectivity of drug assay
  → PK interactions

* mentioned in substance specific guidance of FDA (cyclophosphamide, felbamate

General aspects for studies in patient populations

Design and sample size

- not a healthy collective → restrictions on food or blood volume, more drop-outs (vomiting, SAE, inconvenience)
- Necessity of fasten study → treatment can be administered 2 hrs after a light breakfast in case health conditions prevent fasting*
- necessity of fed study → a light breakfast can be used as fed meal *
- high inter- and intra-subject variability → high sample size needed, replicate design as preferred option **
- possible impact of disease or co-medication on gastro-intestinal absorption → cave: opiode, gastro-intestinal surgery
- steady state necessary → should be proven by at least 3 trough values BE assessment over one dosing interval

* mentioned in substance specific guidance of FDA (doxorubicin, imatinib)
** Reference scaled BE approach mentioned in FDA guidance for
Capecitabine (09/2012)
Altretamine (04/2010)

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General aspects for studies in patient populations

single dose ⟷ steady state

a) drugs with short half life

Capecitabine ($t_{1/2}$ ~ 1hr, twice daily dosing)

Single dose

Additional days		Treatment period		Treatment free period
Day - 2	Day -1	Day 1	Day 2-14	Day 7
⇧	⇧	⇧		

Azathioprine ($t_{1/2}$ ~ 3-5 hrs, once daily dosing)

Single dose

Continuous stable treatment			
Day 1	Day 2	Day 3	
⇧	⇧	⇧	

General aspects for studies in patient populations

single dose ⟷ steady state

b) drugs with normal / long half life

Cyclophosphamide ($t_{1/2}$ ~ 7 hrs)

Steady state (switch-over design)

Treatment period 14 days					+ 1 day
Period 1		Period 2		Period 3	
Day 1	Day 5	Day 1	Day 5	Day 1	Day 5

Clozapine ($t_{1/2}$ ~ 12 hrs)

Steady state (switch-over design)

Continuous stable treatment					
Period 1		Period 2		Period 3	
Day 1	Day 10	Day 1	Day 10	Day 1	Day 10

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Example: Capecitabine

Single dose cross-over, twice daily dosing
patient population: breast cancer (colorectal cancer)

Additional days		Treatment period		Treatment free period
Day - 2	Day -1	Day 1	Day 2-14	Day 7

Estimated sample size
Intra-subject CV*:
AUC ~ 22%
C_{max} ~ 45%

	FDA		EU	
ratio	90 %	95 %	90%	95%
2-way cross-over**	166	81	166	81
semi-replicate***	31	23	40	29

* Cassidy et al., Cancer Chemother Pharmacol 1999, 44; 453-460
** Diletti, 1991
*** Tothfalusi, 2012

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Example: Sunitinib

Multiple dose cross-over
patient population: gastro-intestinal stromal cancer (GIST),
metastatic renal cell carcinoma (MRCC)
half-life: 40 – 60 hrs
steady-state: within 10 -14 days

Treatment period 4 weeks				Treament free period 2 weeks	Treatment period 4 weeks			
Period 1		Period 2			Period 3		Period 4	
Day1	Day14	Day1	Day14		Day1	Day14	Day1	Day14

Estimated sample size
Intra-subject CV*:
AUC / C_{max}~ 29 – 38 %

	FDA		EU	
ratio	90 %	95 %	90%	95%
2-way cross-over**	122	60	122	60
semi-replicate***	33	24	44	29
full-replicate***	24	18	31	20

*FOI, Sunitinib
** Diletti, 1991
*** Tothfalusi, 2012

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Summary

Healthy volunteers ↔ patients

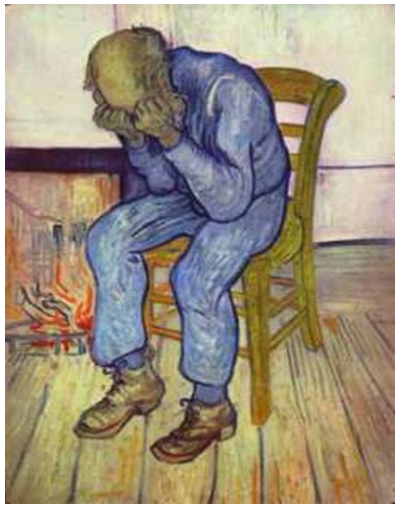
- **Studies in patiens are a challenge due to several restrictions**
- **Study design has to be adapted to labelling requirements**
- **Mostly a high inter and intra subject variability can be expected**

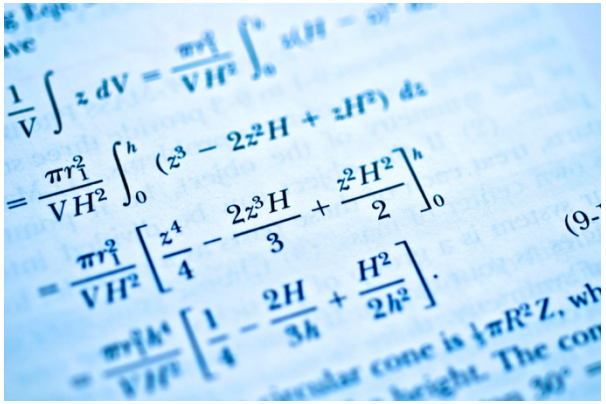
→ **replicate study designs are the preferred option in most of the cases**

→ **sample size needed is lower for US studies than for EU studies**

Thank you very much

for your attention!





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