Bioequivalence of MR Products

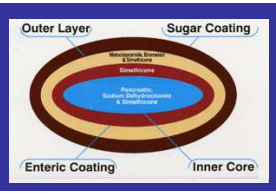
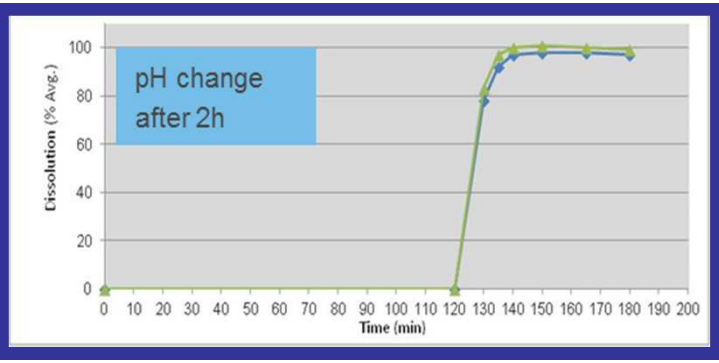
AGAH Conference on the „New European Modified Release Guideline“

Bonn, June 15th, 2015

Disclaimer

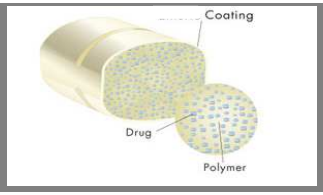
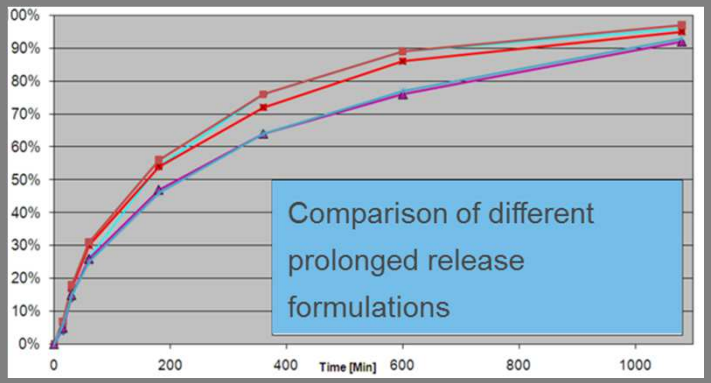
This presentation represents the personal interpretation and opinion of the speaker and should not be interpreted as Teva's perspective or regulatory authorities' requirements.

Studies required for delayed release formulations

Delayed Release	
Single Unit	**Multiple Unit**
Enteric coated tablet	Enteric coated pellets/ minitabs in Capsule/ compressed into tablet
	
	

- Multiple Unit:
  - a single-dose fasting study
  - a single-dose fed study using a high-fat meal
- Single Unit:
  - Additionally, single-dose studies for all strengths under food conditions recommended by SmPC (bracketing approach is possible)

Studies required for prolonged release formulations

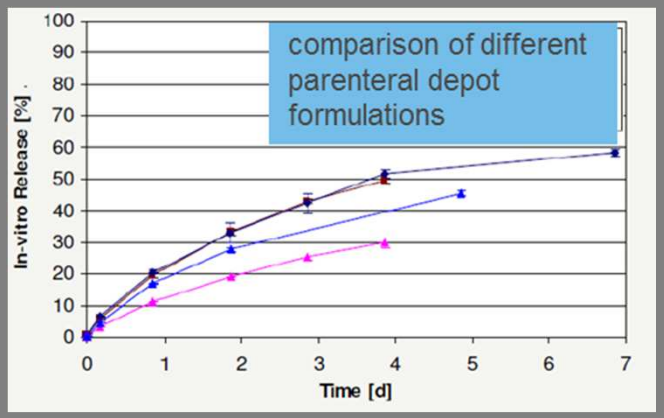
Prolonged Release	
Single Unit	**Multiple Unit**
ER Matrix tablet/ER Coated tablet/OROS	ER Coated pellets/minitabs in Capsule
	
	

- Multiple Unit:
  - a single-dose fasting study
  - a single-dose fed study using a high-fat meal
  - usually, a steady-state (multiple dose) study
- Single Unit:
  - Additionally, single-dose studies for all strengths under food conditions recommended by SmPC (bracketing approach is possible)

Studies required for parenteral depot formulations

Prolonged Release

Depot injections



- a single-dose study
- usually, a steady-state (multiple dose) study

Strength waiver criteria for delayed release formulations

Multiple Unit:

- Study in one strength is sufficient for single dose studies both under fed and fasting conditions if waiver criteria as for IR products are fulfilled

Single Unit:

- Study in one strength is sufficient for single dose study (under food conditions not recommended according to the SmPC)
  - if waiver criteria as for IR products are fulfilled
  - if different strengths have the same shape

Strength Selection:

- Highest / most sensitive strength

Strength waiver: Shape assessment

“However, if the strengths of the test product do not fulfill these criteria or if the different strengths have different shape two strengths representing the most extreme difference should be tested in fed state.”

Discussion for clarification:

- A more detailed definition of „different shape“ (e.g. length to width ratio not differing by more than a certain amount) cannot be given.
- Round vs. triangular or oval vs. diamond are to be considered different shape.

Strength waiver criteria for prolonged release formulations

Multiple Unit:

- Study in one strength is sufficient for single dose and multiple dose studies, if waiver criteria as for IR products are fulfilled

Single Unit:

- Study in one strength is sufficient for single dose (food conditions not recommended according to the SmPC) and multiple dose
  - if waiver criteria as for IR products are fulfilled
  - if different strengths have the same shape (relevant only for s.d. study)

Strength Selection:

- Highest strength for multiple dose study of single unit formulations
- Highest / most sensitive strength for all other studies

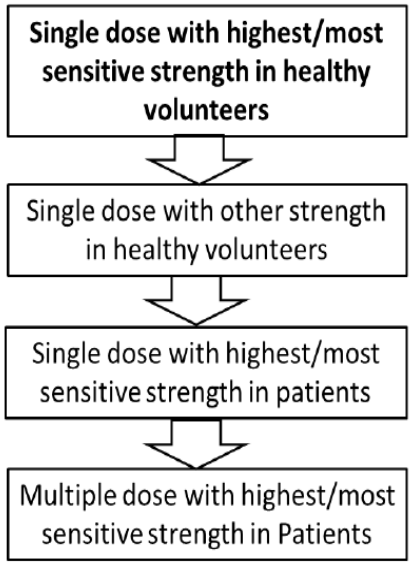
Strength waiver criteria for parenteral depot formulations

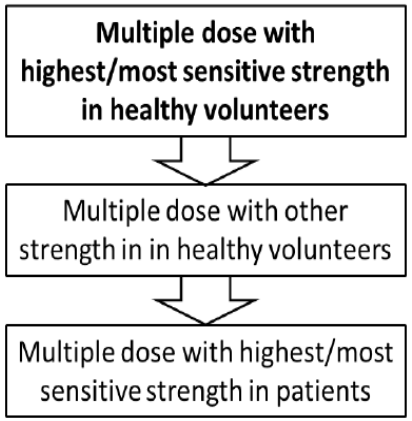
- Study in one strength is sufficient for single dose and multiple dose conditions
  - if the different strengths are proportional in composition
  - if different strengths exhibit a similar dissolution profile

Strength Selection:

- Based on pharmacokinetic linearity and safety -> usually the most sensitive strength
- In case of full proportionality and PK linearity any strength is suitable
- Non-therapeutic doses may be acceptable for safety reasons

Studies in healthy volunteers versus patient studies





"If it is not feasible to conduct single dose studies in patients, these can be replaced by multiple dose studies."

Discussion for clarification:

When single dose studies are not feasible, an additional multiple dose study in patients in the lowest / a lower strength would be expected.

Special aspects in single dose studies: Food effect

Single-dose study design options:

I. One study: 4-way CO: T(fast); T(high-fed); R(fast); R(high-fed)

II. Two studies: 2-way CO: T(fast); R(fast); 3-way CO: T(high-fed); R(high-fed); T(fast)

III. Two studies: 2-way CO: T(fast); R(fast); 2-way CO: T(high-fed); R(high-fed)

Special aspects in single dose studies: Food effect

Discussion for clarification:

- In option I. (4-way crossover) it is acceptable to separate fasting and fed conditions, e.g. fasting in P1 and P2, fed in P3 and P4 -> 2 sequences are sufficient, e.g.
  - T(fasting) – R(fasting) – T(fed) – R(fed)
  - R(fasting) – T(fasting) – R(fed) – T(fed)
- In option II. (3-way crossover) it is expected that the „additional food condition“ is administered in all 3 periods -> 3 / 6 sequences, e.g.
  - T(fed) – R(fed) – T(fasting)
  - R(fed) – T(fasting) – T(fed)
  - T(fasting) – T(fed) – R(fed)

Special aspects in single dose studies: Truncation

"A truncated $AUC_{(0\text{-}72h)}$ is not acceptable for MR products."

Discussion for clarification:

- Truncation after 120h may be acceptable for many orally applied MR products, but this cannot be used as a general rule.
- For non-orally applied MR products with very long half-life it may be acceptable (but only case-by-case), in order to avoid very long study duration, to truncate at a time point where < 80% of AUC(0-∞) is covered by AUC(0-t), if elimination is in the linear range.

Special aspects in ss studies: Fed conditions

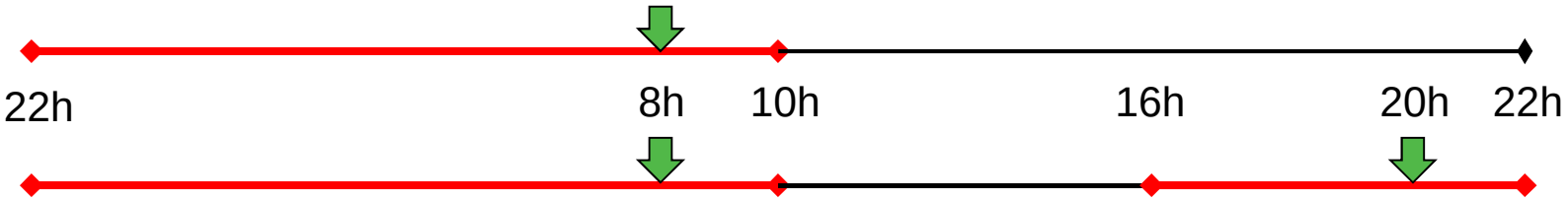
"If the SmPC states that the product has to be taken in fed conditions only the study should be performed in fed conditions (standard meal) including the day of profiling."

Discussion for clarification:

- Standardization is in the interest of the sponsor, so it is recommended to define a target range for the standard meal in terms of calories and fat / protein / carbohydrate content
- Same meals during different periods contribute to standardization
- Subjects who do not eat their meals completely do not have to be excluded from the study (preferably to be described in the protocol)
- Different rules during titration and prior to profiling are acceptable

Special aspects in ss studies: Fasting conditions

"Fasting conditions in a multiple dose study need to be adapted to realistic situations, i.e. morning administration requires a 10 hour fasting interval whereas for all other administrations 4 hour fasting prior to administration is sufficient. Fasting after each administration should be defined as 2 hours minimum."



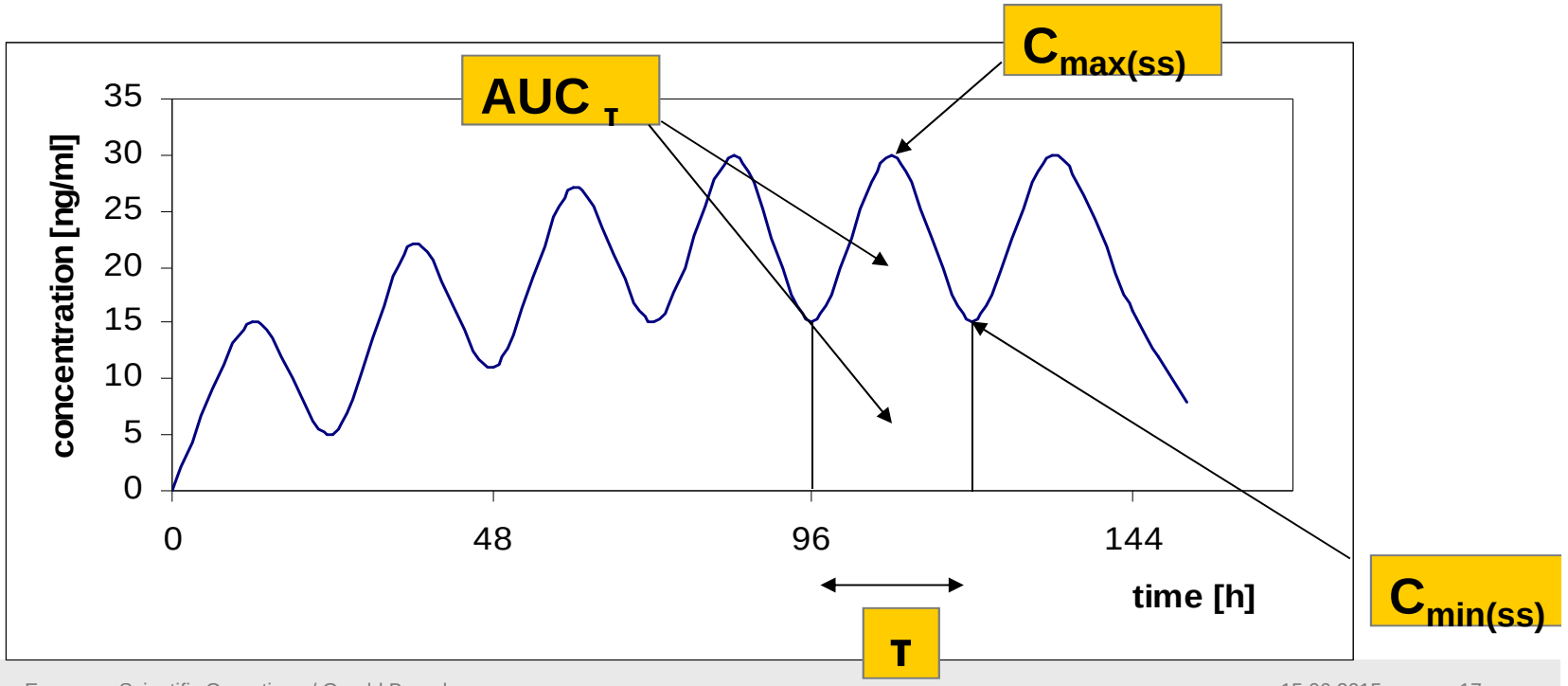
Special aspects in ss studies: Fasting conditions

Discussion for clarification:

- Since it is sometimes difficult to follow these strict rules during the whole study period, it is acceptable to deviate in certain situations, e.g.
  - in patient studies,
  - more than once daily administration,
  - long titration periods.
- Stricter rules for standardization prior to profiling than in the early titration period are acceptable.

Special aspects in ss studies: Determination of ss

"Whether the steady-state has been achieved is assessed by comparing at least three pre-dose concentrations for each formulation."



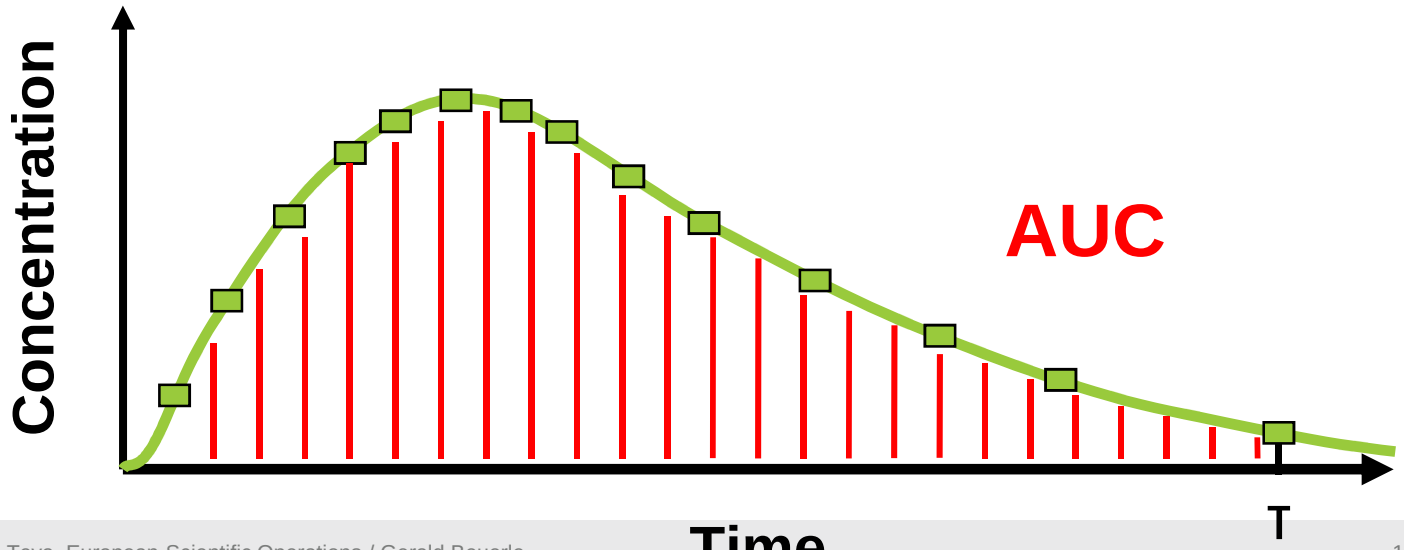
Special aspects in ss studies: Determination of ss

Discussion for clarification:

- c_τ (concentration at the end of the dosing interval used for profiling) can also be considered as “pre-dose value”
- No statistical analysis is expected for assessment of steady state
- Main criterion is if theoretical assumptions for reaching steady state based on half-life are kept
- Additionally, visual comparison of trough values
- No change compared to previous guideline requirements

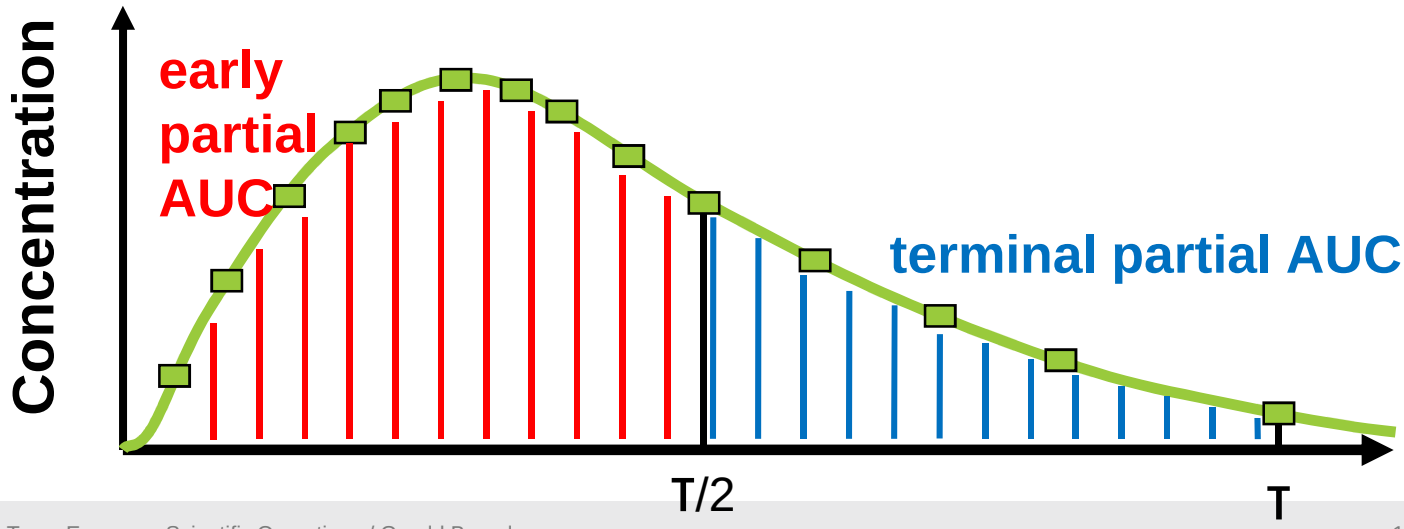
Special aspects in ss studies: Waiver of ss studies

"A multiple dose study is needed unless a single dose study has been performed with the highest strength which has demonstrated that the mean $AUC_{(0-\tau)}$ after the first dose covers more than 90% of mean $AUC_{(0-\infty)}$ for both test and reference, and consequently a low extent of accumulation is expected."



Special aspects in ss studies: Waiver of ss studies

"An early $_{partial}AUC_{(0 – cut\text{-}off\ t)}$ and a terminal $_{partial}AUC_{(cut\text{-}off\ t\ -\ tlast)}$, separated by a predefined cut-off time point, e.g. half of the dosage interval is recommended, unless otherwise scientifically justified."



Special aspects in ss studies: Waiver of ss studies

Discussion for clarification:

Other cut-off points are acceptable if scientifically justified, no need for Scientific Advice.

Bracketing approach

“In case bioequivalence assessment at more than two strengths is needed, e.g. because of deviation from proportional composition and/or if dissolution profiles are not similar, or for single unit formulations with proportional composition, a bracketing approach may be used if the other waiver criteria (see Guideline on the investigation of bioequivalence CPMP/EWP/QWP/1401/98) are fulfilled. In this situation it can be acceptable to conduct two bioequivalence studies, if the strengths selected represent the extremes, e.g. the highest and the lowest strength or the two strengths differing most in composition, dissolution or shape, so that any differences in composition or dissolution in the remaining strengths is covered by the two conducted studies.”

Bracketing approach

"In case bioequivalence assessment at more than two strengths is needed, e.g. because of deviation from proportional composition and/or if dissolution profiles are not similar, or for single unit formulations with proportional composition, a bracketing approach may be used if the other waiver criteria (see Guideline on the investigation of bioequivalence CPMP/EWP/QWP/1401/98) are fulfilled. In this situation it can be acceptable to conduct two bioequivalence studies, if the strengths selected represent the extremes, e.g. the highest and the lowest strength or the two strengths differing most in composition, dissolution or shape, so that any differences in composition or dissolution in the remaining strengths is covered by the two conducted studies."

Bracketing approach

"In case bioequivalence assessment at more than two strengths is needed, e.g. ***because of deviation from proportional composition*** *and/or if dissolution profiles are not similar,* ***or for single unit formulations with proportional composition****, a bracketing approach may be used if the other waiver criteria (see Guideline on the investigation of bioequivalence CPMP/EWP/QWP/1401/98) are fulfilled. In this situation it can be acceptable to conduct two bioequivalence studies, if the strengths selected represent the extremes, e.g. the highest and the lowest strength or the two strengths differing most in composition, dissolution or shape, so that any differences in composition or dissolution in the remaining strengths is covered by the two conducted studies."*

Bracketing approach, immediate release

	mg	%	mg	%	mg	%	mg	%	mg	%
API	**100**	50%	**75**	37,5%	**50**	25%	**25**	12,5%	**12,5**	6,25%
Filler	60	30%	85	42,5%	110	55%	135	67,5%	147,5	73,75%
Binder	9	4,5%	9	4,5%	9	4,5%	9	4,5%	9	4,5%
Disintegrant	20	10%	20	10%	20	10%	20	10%	20	10%
Lubricant	1	0,5%	1	0,5%	1	0,5%	1	0,5%	1	0,5%
Film Coat	10	5%	10	5%	10	5%	10	5%	10	5%
Total	**200**	100%	**200**	100%	**200**	100%	**200**	100%	**200**	100%

Bracketing approach is useful

Bracketing approach, immediate release

	mg	%	mg	%	mg	%	mg	%
API	**100**	50%	**75**	37,5%	**50**	50%	**25**	25%
Filler	70	35%	95	47,5%	35	35%	60	60%
Binder	9	4,5%	9	4,5%	4,5	4,5%	4,5	4,5%
Disintegrant	10	5%	10	5%	5	5,0%	5	5%
Lubricant	1,0	0,5%	1,0	0,5%	0,5	0,5%	0,5	0,5%
Film Coat	10	5%	10	5%	5	5%	5	5%
Total	**200**	100%	**200**	100%	**100**	100%	**100**	100%

Bracketing approach could be useful, but the extremes are not clearly defined

Bracketing approach, immediate release

	mg	%	mg	%	mg	%	mg	%
API	**100**	25%	**75**	25%	**50**	25%	**25**	25%
Filler	220	55%	165	55%	110	55%	55	55%
Binder	18	4,5%	13,5	4,5%	9	4,5%	4,5	4,5%
Disintegrant A	20	5,0%	20	6,7%	15	7,5%	8	8,0%
Disintegrant B	20	5,0%	10	3,3%	5	2,5%	2	2,0%
Lubricant	2	0,5%	1,5	0,5%	1	0,5%	0,5	0,5%
Film Coat	20	5%	15	5%	10	5%	5	5%
Total	**400**	100%	**300**	100%	**200**	100%	**100**	100%

Bracketing approach is useful

Bracketing approach

“However, for prolonged release formulations release-controlling excipients and mechanism should be the same for all strengths of the test product. The same is required for release controlling coatings for delayed release formulations.”

Discussion for clarification:

- Release-controlling agents should be qualitatively the same, not quantitatively.
- E.g. proportional
- Non-proportional is also acceptable, then the intermediate strengths need to have an intermediate composition of release-controlling agents (in a comparable ratio?).

Bracketing approach, modified release, single unit

	mg	%	mg	%	mg	%	mg	%
API	**100**	25%	**75**	25%	**50**	25%	**25**	25%
Filler	220	55%	165	55%	110	55%	55	55%
Binder	18	4,5%	13,5	4,5%	9	4,5%	4,5	4,5%
Release Contr.	40	10,0%	30	10,0%	20	10,0%	10	10,0%
Lubricant	2	0,5%	1,5	0,5%	1	0,5%	0,5	0,5%
Film Coat	20	5%	15	5%	10	5%	5	5%
Total	**400**	100%	**300**	100%	**200**	100%	**100**	100%

Bracketing approach is useful

Bracketing approach, modified release, single unit

	mg	%	mg	%	mg	%	mg	%
API	**100**	25%	**75**	25%	**50**	25%	**25**	25%
Filler	220	55%	160	53%	100	50%	45	45%
Binder	18	4,5%	13,5	4,5%	9	4,5%	4,5	4,5%
Release Contr.	40	10,0%	35	11,7%	30	15,0%	20	20,0%
Lubricant	2	0,5%	1,5	0,5%	1	0,5%	0,5	0,5%
Film Coat	20	5%	15	5%	10	5%	5	5%
Total	400	100%	300	100%	200	100%	100	100%

Bracketing approach may be acceptable (?)

Bracketing approach, modified release, single unit

	mg	%	mg	%	mg	%	mg	%
API	**100**	25%	**75**	25%	**50**	25%	**25**	25%
Filler	220	55%	165	55%	110	55%	55	55%
Binder	18	4,5%	13,5	4,5%	9	4,5%	4,5	4,5%
Release Contr. A	20	5,0%	20	6,7%	15	7,5%	8	8,0%
Release Contr. B	20	5,0%	10	3,3%	5	2,5%	2	2,0%
Lubricant	2	0,5%	1,5	0,5%	1	0,5%	0,5	0,5%
Film Coat	20	5%	15	5%	10	5%	5	5%
Total	400	100%	300	100%	200	100%	100	100%

Bracketing approach may not be acceptable (?)

New strength for an already approved product

“Section 6 also applies to the development of a new strength within the existing dose range according to the SmPC of the reference product.
For a new strength with proportional composition to approved strength(s) a bracketing approach may be applicable.
For a new strength with non-proportional composition to approved strength(s), the new strength has to meet the requirements as described in relevant sections above (section 6.1-6.5).”

Discussion for clarification:

In situations where an additional study is needed, but the reference dose cannot be administered through combination of available strengths, an attempt should be made to come as close as possible and perform a dose-corrected evaluation (in case of linear PK).

Ethanol dose dumping (in vitro)

"For generic oral formulations, in vitro studies of the release in alcohol solutions should be performed."

Discussion for clarification:

- Testing in 40% also requested
- Acidic pH (1.2) preferred over QC medium
- Initial phase would be sufficient in case of complex release media simulating first the gastric environment (2 hours at pH 1.2)