BfArM

EMA/EGA

Session 1: orally administered Modified Release Products

European Regulatory Requirements

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Disclaimer

The presentation reflects the personal opinion of the author and not necessarily the official policy of the EMA or national agency

The Revised Guideline

- **Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms** *(EMA/CPMP/EWP/280/96 Corr1)*
- **Product specific bioequivalence guidances??**

Structure of the guideline

- ***Three main sections***
  - *Applications for modified release forms of new chemical entities*
  - Application for a modified release formulation of a drug that is authorised as an immediate release formulation (e.g. *line extensions*)
  - *Application for modified release forms bioequivalent to a marketed modified release form* (i.e. *generics*)

Types of modified release and dosage forms (DF) (focussing on oral DF)

sect 1.1

- Prolonged release DF
- Delayed release DF
- Multiphasic release DF
  - *Biphasic release*
  - *Pulsatile release*

- ***Multiple unit DF***
- ***Single unit DF***

Applications for modified release forms of new chemical entities ('NDA')

Just to mention (sect 4)

- Biopharmaceutic performance (see sect 4.1)
- Remains a full application
- ***Robustness (food, alcohol)***
- IVIVC – if possible (ref. to appendix III)

'NDA'-Food Effect: Safety, Efficacy,…(ref. sect 5)

- **Food effect in an efficacy & safety perspective**
- **More studies may be required**
  - Dose recommendations regarding meals
    - different types of food
    - administration at certain time intervals 'pre' or 'post' meal (*cave:* ***SmPC recommendations***!)
  - Different type of administrations e.g. sprinkle on soft foods or dispersion in water
    - additional *in-vitro* dissolution testing e.g., open vs intact formulation
    - appropriate *in-vivo* studies, *unless otherwise justified*

'NDA'-Dose dumping and effect of alcohol

(ref. sect 5)

- **Unexpected release of MR form should be excluded!**
  - Dose dumping poses risk reg. safety and diminished efficacy due to:
    - biopharmaceutical quality deficiencies
    - prolonged gastric residence time
      (cave: *monolithic dosage forms*)
    - effects of ***alcohol*** (cave: *methods*?!)

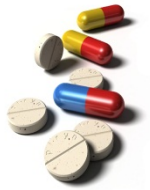
Abridged application *(ref. sect 6)* ***defining a GENERIC***

- A generic medicinal product is defined as a medicinal product that has:
  - the same qualitative and quantitative composition in active substance(s) as the reference product,
  - the *same pharmaceutical form* as the reference medicinal product,
  - and whose bioequivalence with the reference medicinal product has been demonstrated by *appropriate* bioavailability studies. (*acc. to Directive 2001/83/EC as amended*)

- Which and/or how many bioavailability studies are considered appropriate for which MR dosage forms for demonstrating bioequivalence?

BE in abridged application *(ref. sect 6)*

General comments (see sect. 6):

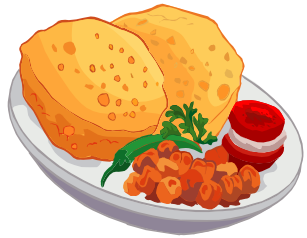


- Test and reference should have *the same pharmaceutical form* - but
- Differences in the release controlling excipients and/or mechanism may not prevent a generic application if bioequivalence can be demonstrated in the *fasted & fed* state and (if needed) under *steady-state* conditions

BE in abridged application – single dose fasted/fed study(ies)

- *See section 5.1.4.1 (experimental conditions), app IV (Summary of study recommendations for abridged applications) and sect. 6.1.1.1 for recommended schemes*
  - Ultimate goal is proving biopharmaceutic similarity and robustness under any condition
  - Fed condition: usually high-fat, high-calorie meal immediately before dosing – or other timing depending on SmPC recommendation of the originator product

- *Personal note: can not be done in-vitro!*



BE in abridged application – steady-state study?!

- ***new*: see 6.1.1.2. -** steady-state studies may be waived if accumulation is very low or can be excluded, i.e. AUC within the dosing interval covers more than 90% of AUCinf

- In case of waiving the steady-state study, additional shape characteristics have to be used: **partial AUCs**!

BE in abridged application – single unit DF

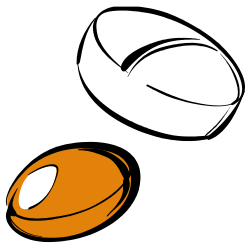
Strength(s) to be investigated for ***single-unit prolonged release*** formulations (see sect. 6.1.2.1):

- *Single-unit* formulations require single-dose studies for *all* strengths – **new**: bracketing approach can be considered!
- Depending on the SmPC recommended intake, *further* (fed or fasted, *e.g*. the non-recommended) single-dose studies are requested with the highest strength only if usual proportionality requirements (see 4.1.6 in BE GI 1401/98) are fulfilled.

BE in abridged application – single unit DF

Strength(s) to be investigated for ***single-unit prolonged release*** formulations (see sect. 6.1.2.1) contd.:

- ‘Bracketing’ option in case of non-proportional product series or if proportional products differ in shape: identify and investigate the ‘***extreme***’
- *Are there any other/further differences relevant for bioavailability?*



  - *e.g. surface area/volume ratio may influence AUC?*
  - *Size is likely differing between strengths?*

BE in abridged application – single unit DF

Strength(s) to be investigated for ***single-unit prolonged release*** formulations (see sect. 6.1.2.1) contd.:

- **Multiple-dose** *(i.e. steady state)* **studies** are requested (***if needed***) at least using the highest strength in case of proportional product series – the ***most sensitive*** for non-proportional products

BE in abridged application – multiple unit DF

Strength(s) to be investigated for ***multiple-unit prolonged release*** formulations (see sect. 6.1.2.2.):

- Comparative studies (i.e. fed/fasted/md) are acceptable using one strength if compositions are proportional and different strengths contain identical beads or pellets – *and dissolution profiles are similar (- with reference to the bioequivalence Gl 1401/98 –*)

BE in abridged applications

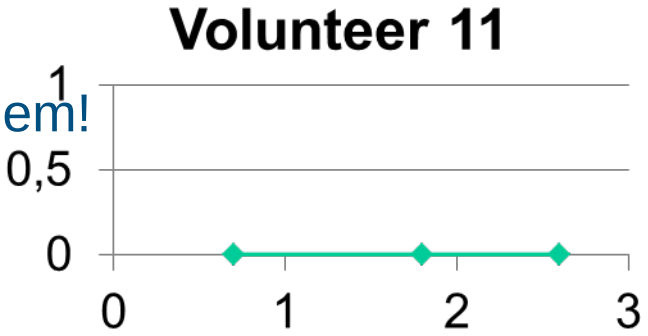
Strength(s) to be investigated for *delayed release*, gastro-resistant formulations (see sect. 6.2.) **:**

- Single-dose studies in the fasted and fed state requested but *no* steady-state studies
- Same principles as for prolonged release apply regarding *single- and multiple unit* formulations
  - 'extremes'! in case of multiple strengths
  - Of note: **two** sd studies for **two** single unit omeprazol strengths
  - ***Cave***: proportionality of gastro-resistant coating should be considered with respect to surface area (not to core weight), *i.e.* coating layer in mg/cm² surface

BE in abridged applications

Strength(s) to be investigated for *delayed release*, gastro-resistant formulations (see sect. 6.2.3) *contd*.**:**

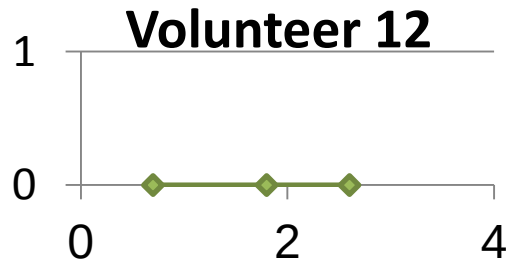
- ***New*** (taken from Q&A): note section 6.2.3 on specific considerations regarding the prolonged residence time in the stomach – 'non-existing' profiles ("outlier") and sampling period – respective 'data' can be excluded from statistics if pre-specified (➥less subjects!)
  - not necessarily a regulatory problem!



BE in abridged applications

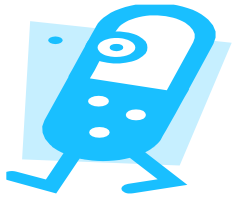
Strength(s) to be investigated for *delayed release*, gastro-resistant formulations (see sect. 6.2.3) *contd*.:

- Regarding 'non-existing' profiles ("outlier") and sampling period
  - Are monolithic enteric coated products avoidable?
  - How to evaluate 'comparable frequency' of 'outliers?
  - **How long is the 'sufficiently long' sampling period**
  - *In-vitro* dissolution convincing?



BE in abridged applications

Strength(s) to be investigated for *multiphasic* formulations (see sect. 6.3) :



- ***New* statement:**

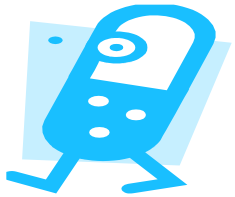
"If one of the release phases is prolonged, the type of studies required are those described in section 6.1"

  - ➡ dealing with formulation effects of a modified release product!

- ***Cave*:** sampling scheme in BE studies, shape evaluation, partial AUCs to cover initial phases

BE in abridged applications

Strength(s) to be investigated for *multiphasic* formulations (see sect. 6.3) **:**



- ***Cave*: the biphasic PK should appropriately be considered; ref. to section 6.8.1 (truncating for partial AUCs must be pre-specified; still No.11 in Q&A Rev.11, 22 January 2015)**

Bracketing Approach *(see sect.6.6)*

- how similar is (sufficiently) similar?
- need to know versus nice to know?

Bracketing Approach *(see sect.6.6)*

- *Bracketing approach may be used in case of deviation from proportionality OR in case of proportional single unit formulations where the other waiver criteria are fulfilled (ref. to BE GI 1401/98)*
- *Investigate* ***extremes*** *in terms of composition and/or dissolution and/or shape*
- *Release controlling excipients (including coatings) and mechanism should be the same for all strengths*

Parameter & Evaluation

- *Need* for multiple dose studies, *i.e.* steady-state conditions
- PK parameters to characterise the ***"shape"*** of plasma profiles

Why are steady-state studies needed? (1)

Steady-state studies are necessary in prolonged release products because:

- Single dose studies, comparing C_{max}, AUC_{0-t} and AUC_{0-inf}, do not provide information about the final phase of release, which reflects the absorption rate / release rate of the formulation since absorption is slower than elimination
  - Tmax may be on the plateau
  - Cmax and AUC may be similar with different shape

- ***But only if there is accumulation***

Why are steady-state studies needed? (2)

- Review of 'real' data showed that C_t in the single dose study might be not predictive of $C_{t,ss}$ in the steady-state study and it is highly variable.
  - García-Arieta A. et al., Investigation on the need of multiple dose bioequivalence studies for prolonged-release generic products. Int J Pharm. 2012 Feb 28;423(2):321-5.
- If it were mandatory, single dose studies would need much higher sample sizes.
- If it were voluntarily, we do not have enough experience to conclude it is predictive.
  - Limitations of simulation studies
  - What if the differences occur after the dosing interval?

Recommendation *(supported by published data)*

- ***"Steady state studies could be considered …***
  - *when MR products have high accumulation*
  - *when the variability is higher for clearance than for drug release*
  - *when differing drug release characteristics would be amplified in the steady state, notably in differing minimum concentrations*
    - Non-linear PK

- Endrenyi L. and Tothfalusi L. Metrics for the evaluation of bioequivalence of modified-release formulations. AAPS J 2012. 14(4):813-819

In case of low extent of accumulation

- Since differences in shape may not be detected with AUC and C_{max} only, **bioequivalence needs to be demonstrated for *additional parameters* representing the *shape*** of the plasma concentration versus time curve **in the single dose study** (see also section 6.8.2)

Parameters: Single dose studies (1)

- in ***single dose*** bioequivalence studies, **$AUC_{(0-t)}$, $AUC_{(0-\infty)}$, residual area, Cmax , $_{partial}AUC$ and tmax** should be determined

- General note: **"truncated" $AUC_{(0-72h)}$ is not acceptable for MR products** *(see 6.8.1.1.)*

Parameters: Single dose studies (2)

- for **multiphasic** modified release products additional parameters to be determined include **$_{partial}$AUC, Cmax and tmax in *all phases***

- the **time point for truncating the $_{partial}$AUC** should be **based on the PK profile for the IR and the MR parts respectively** and should be **justified and pre-specified** in the study protocol

Parameters: Steady state studies

- in ***steady state*** bioequivalence studies**, $AUC_{(0-T)}$, $t_{max,ss}$, $C_{max,ss}$, $C_{T,ss}$, and fluctuation** should be determined

- in contrast to the need of characterisation of **$C_{min,ss}$ for new MR formulations,** a comparison of **$C_{T,ss}$,** which **is easier ("clearer")** to determine, should be **sufficient for generics**

Acceptance criteria *(sect. 6.8.2.2.)*

- The bioequivalence approach considering usual acceptance limits (**80 – 125 %**) is applicable for generic MR products (see CPMP/EWP/QWP/1401/98)
- Any widening of the acceptance criteria for **Cmax** should follow the recommendations on **highly variable drug products** in the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98) – “scaling”.
- A **similar approach** can be used for widening the acceptance criteria for **$C_{max,ss}$, $C_{T,ss}$, and $_{partial}$AUC**

Some Issues that Deserve Consideration

- Comparative in-vitro dissolution for bracketing and proportionality waiver with reference to BE Gl 1401/98 – role of pH 1.2, 4.5 and 6.8 – interpretation and predictability ("***biorelevance***"?!)

- Experience with appropriate bracketing approach for modified release formulations: identifying ***extremes!***
- *Of note:* see appendix 3 on *IVIVC*

Thank you for your attention!