Revised guideline on bioequivalence

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Outline

- Revision of bioequivalence guideline as an example of
  - how need for revision of an EU guideline is identified
  - process for revision
    - consultation
    - discussion

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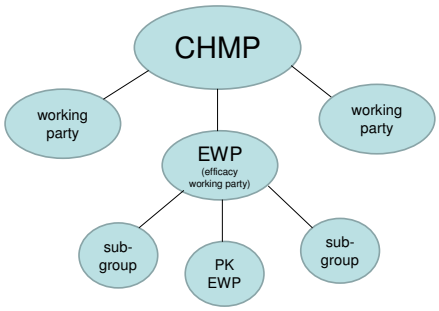

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EWP PK subgroup

- Tasks
  - prepare, review and update EU PK guidelines
  - provide advice to committees (CHMP, CMDh, PDCO, SAWP) on general and product-specific matters relating to PK
  - provide training on PK assessment
- Constitution
  - 10 members: SE, NL, ES, PT, DE, FR, UK, HU, BE
  - Additional experts: DK, AT

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EU bioequivalence guideline

- Present guideline adopted 2001
  - CPMP/EWP/QWP/1401/98
- Some issues interpreted differently by different member states
  - disagreement regarding approvability of MAAs
  - CMD(h) has requested clarification on several issues from PK EWP

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Questions & Answer Document

- Clarification of BE guideline recommendations
  - EMEA/CHMP/EWP/40326/2006
- Widening of acceptance criteria for C_{max} ratio
- Dose and strength to study for non-linear compounds
- Use of metabolite data
- Use of urinary data
- Fasting or fed state
- Use of non-parametric statistical models
- Handling of outliers

Other issues

- Single vs multiple dose study
- Active metabolite in addition to parent
- Prodrugs: inactive parent or active metabolite
- Definition of linearity/non-linearity
- Strength and dose in BE study
- ……

Different interpretations of present guideline

QUALITY ⟷ **CLINICAL RELEVANCE**

- **Q&A insufficient**
- **Revision of guideline needed**
- **PK EWP agreed to QUALITY approach**

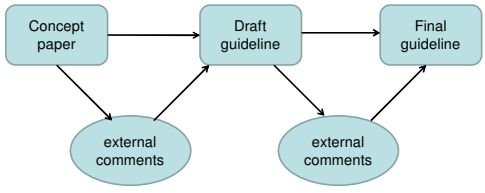
Reasons for revising BA/BE guideline

- Guidance on bioequivalence needs further harmonisation within EU
  - Present guideline interpreted differently by different agencies
    - Some recommendations fairly vague
- New pharmaceutical legislation
  - New definition of generics
- Add recommendations on BCS-based biowaivers

Aim with BE guideline revision

- Simplify
- More clear advice
- Less risk for different interpretation
- Fewer procedures with disagreement between MS

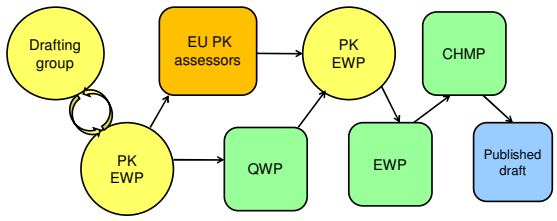
Revision process



Revision process

- Concept paper
  - Provides rationale for revision
  - Lists areas at need for revision
  - Released for comments
- Draft guideline
  - Developed based on concept paper and additional external comments
  - Released for consultation
    - Comments to be provided by industry and interested parties
- Final guideline
  - Revised based on external comments

BE guideline revision



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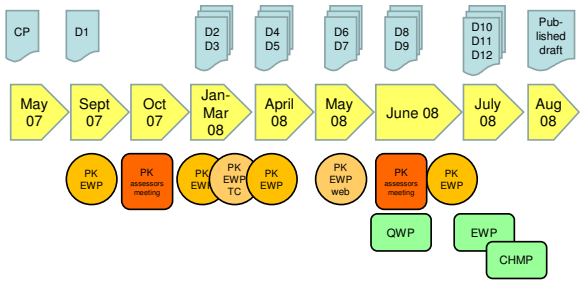

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European Medicines Agency
Pre-Authorisation Evaluation of Medicines for Human Use

London, 24 July 2008
Doc. Ref. CPMP/EWP/QWP/1401/98 Rev. 1

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

DRAFT

GUIDELINE ON THE INVESTIGATION OF BIOEQUIVALENCE

DRAFT AGREED BY THE EFFICACY WORKING PARTY	July 2008
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	24 July 2008
END OF CONSULTATION (DEADLINE FOR COMMENTS)	31 January 2009

http://www.emea.europa.eu/htms/human/humanguidelines/efficacy.htm
http://www.emea.europa.eu/pdfs/human/qwp/140198enrev1.pdf

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Revision of BE guideline

- Concept paper May 2007
  - Revision of BA/BE guideline
  - BCS-based Biowaiver (Annex to BA/BE guideline)
- Draft BE guideline released for consultation Aug 2008
  - http://www.emea.europa.eu/htms/human/humanguidelines/efficacy.htm
  - http://www.emea.europa.eu/pdfs/human/qwp/140198enrev1.pdf
- End of consultation 31 January 2009
  - Send comments to EWPSecretariat@emea.europa.eu using specific template

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Consultation period

- Interaction with external parties
- Bioequivalence conferences
  - Krakow Oct 08
  - Prague Oct 08
  - EGA meeting Paris Oct 08
  - Eufeps meeting Bonn Jan 09

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Concluding remark - Revised BE guideline

- Aim to give more clear recommendations partly reached
- Complex issues
  - when to conduct additional multiple dose study
  - when to measure active metabolite
  - which strength(s) and dose(s) to evaluate
  - narrow therapeutic index drugs
  - highly variable drugs……
- Industry is expected to have many comments
- → Possibly extensive revision during finalisation

Concluding remark

- Guidelines are written both for industry and regulators
  - provide industry with requirements/recommendations for study design and conduct
  - ensure common view among EU regulators
- Development and revision of guidelines can be a complex process
  - can involve several steps and many interested parties

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Thank you!