Assessment of Bioequivalence Studies from regulatory perspective

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Consolidated Directive 2001/83

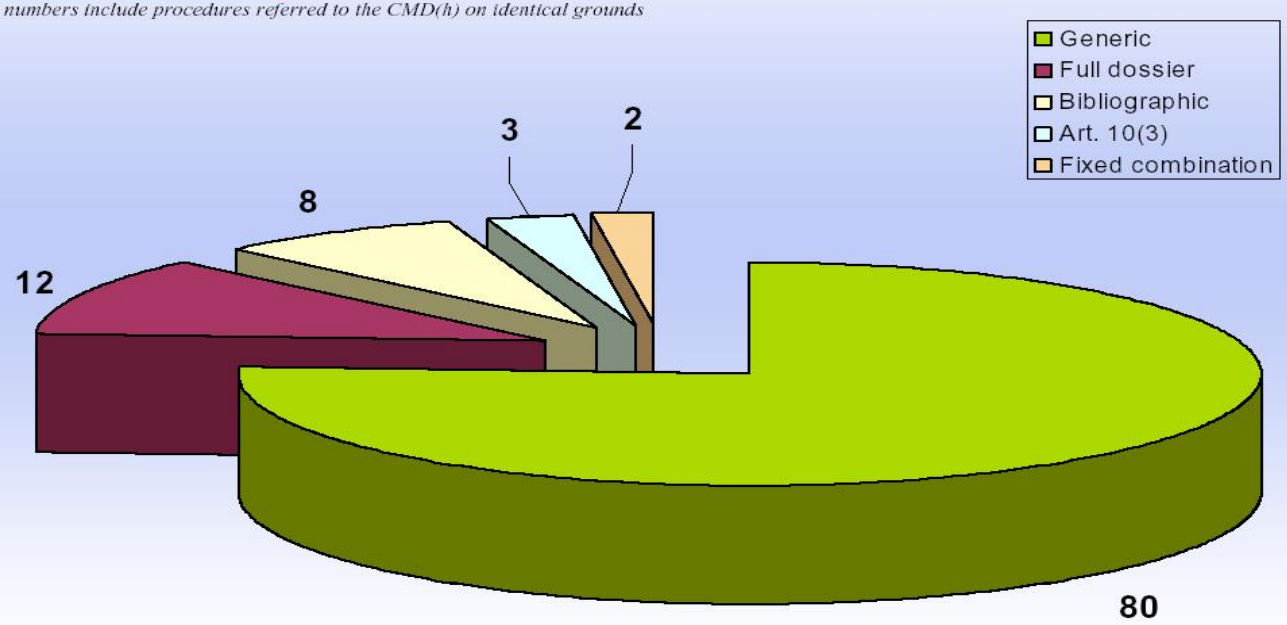
- **Generic Medicinal Product – medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies**

Referrals to CMD(h) in 2006

Co-ordination Group for Mutual Recognition and Decentralised Procedures - Human

Per Legal Basis*

**The numbers include procedures referred to the CMD(h) on identical grounds*



MRP/DCP and CMD(h) referrals – Statistics for 2006

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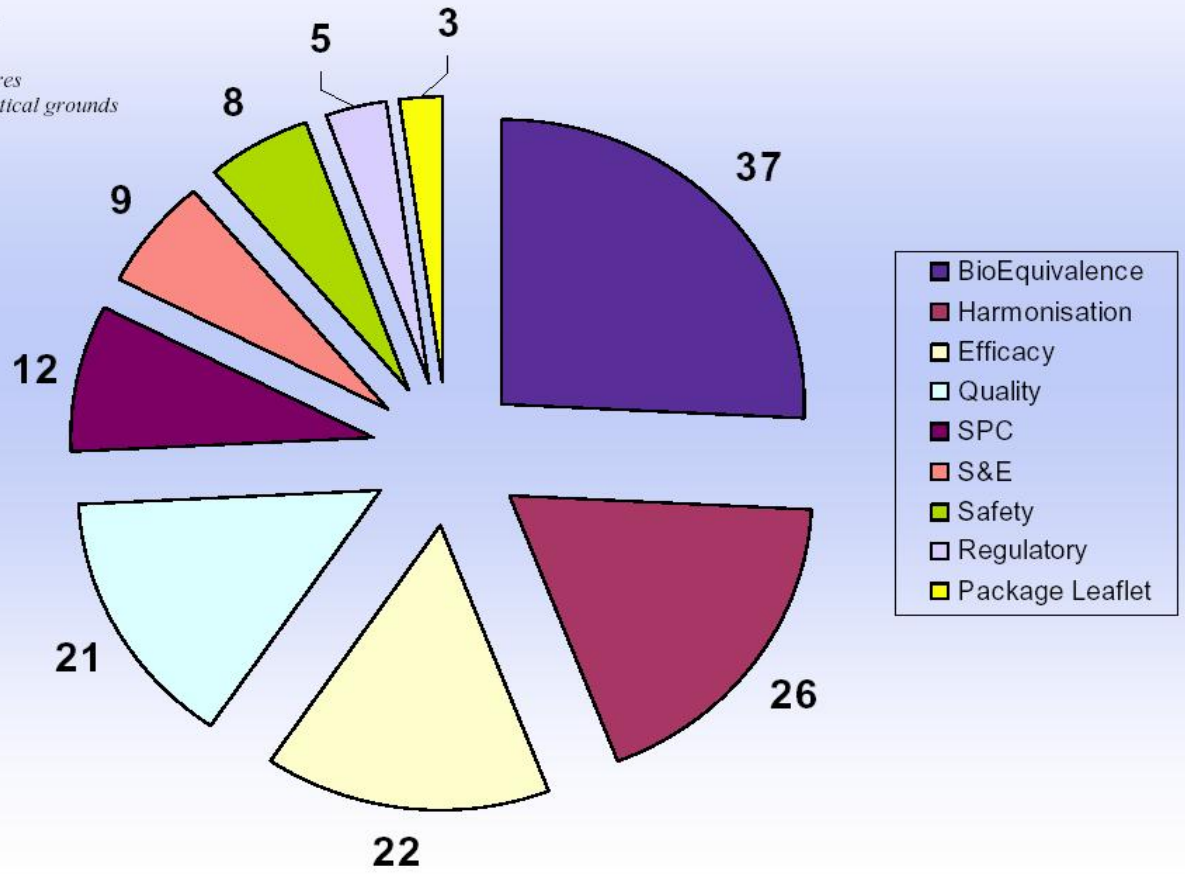

MRP/DCP and CMD(h) referrals – Statistics for 2006

Referral to CMD(h) reasons

- **Different views on the clinical consequences of deviation from the existing BE guideline**
- **Different interpretation of the submitted data concerning safety and efficacy of the medicinal product**

PROBLEMS

- Guidelines
- Good studies and reports from companies
- Uniformity of assessment
- Enlargement of EU

Reference Product

- **Definition – Medicinal product authorized under art.6 in accordance with the provisions of art.8**
- **Comparator Pharmaceutical Product QAS/05.143/rev.1**

Reference Product

- Only products from EU
- Ideal – one product for EU
- What product should you take?
- Discriminatory dissolution test
- More BE studies?

Choice of referent product

- **The innovator product is the most logical comparator product for a generic product because of quality, safety and efficacy should have been well assessed and documented in pre-marketing studies and post-marketing monitoring schemes.**
- **For some medicinal product an innovator cannot be identified; in some cases an innovator product is not available on the market.**

Choice of Reference product

- **A selection of the reference product is usually made at the national level by drug regulatory authority.**
- **The choice of reference product should be justified by the applicant**
- **For an abridged application claiming essential similarity to a reference product, applicant to MSs based on BE with reference product from one MS can be made**
- **When additional BE studies are required, they should be carried out using the product registered in the concerned MS as the reference product**

Problems

- **Despite a common scientific basis supporting BE, no harmonization between different MS agencies in terms of BE requirements**
- **Guidance documents are somewhat vague with regards to many aspects related to study design, conduct and PK and statistical analysis of BE studies**

Guidances

- **Note for guidance on the investigation on bioavailability and bioequivalence 2002**
- **Question and Answers on the Bioavailability and Bioequivalence Guideline 2006**
- **Reflection paper for HVD**

General BE criteria

- **AUCt: 90% CI must be between 80-125%**
- **Cmax: 90% CI must be between 80-125%**
- **Wider interval may be acceptable (e.g. 75 – 133%) with proper efficacy and safety justification**

Problem Issue 1

"In certain cases? a wider interval may be acceptable. The interval must be prospectively defined e.g. 0.75 – 1.33 and justified addressing in particular any safety or efficacy concerns for patients switched between formulations."

Use of wider acceptance criteria for Cmax

- **The use of wider acceptance criteria is a common source of questions or deficiencies coming from the different regulatory agencies within Europe**
- **Inappropriate clinical justification of the use of wider acceptance criteria for Cmax parameter**
- **Criteria not properly defined *a priori* in protocol**
- **Some EU agencies are reluctant to accept wider criteria for Cmax parameter**

Medicines with narrow therapeutic range

- **AUCt, Cmax**

Acceptance interval need to be tightened

What type of studies must be performed - Design of studies

Need for fed studies may not always

be clear

Immediate-release formulation – Total 1-2 studies: 1 single dose croos-over study, fasted and/or fed condition according to SmPC recommendations connected with food interaction effects

Do we need BE studies with different immediate release formulations ??? /e.g. tablets and capsules/

What type of studies must be performed - Design of studies

- **Modified-release formulation**

Total 3 studies

1 single dose crossover study fasted

1 single dose crossover study fed

1 steady state study

Problem issue 2 METABOLITES

Theory:

BE should typically be based upon the parent compound.

Does the metabolite need to be measured?

Should BE criteria be applied to both parent and/or metabolite?

Problem issue 2 METABOLITES

Metabolite: when?

- **Instead of parent: if concentrations of parent are too low characterise the PK**
- **Additionally to parent: if metabolites significantly contribute to the net activity of an active substance and the PK of the system is non linear(evaluate them separately)**

Practice:

- **Some European agencies have accepted BE based on metabolites**
- **Some European agencies have required active metabolite evaluation, even when PK system is linear**

Problem issue 3

- **Endogenous medicinal product**

Not addressed in general BE/BA guidance from EMEA

Require special considerations that must be addressed on case by case basis

Endogenous compounds with specific recommendations – estradaiol, testosterone, progesterone, calcitriol etc.

What are the issues with endogenous medicinal products

- **Discrimination between endogenous and exogenous sources**
- **Feedback inhibition mechanisms of endogenous production in the body and circadian rhythm**
- **Assay sensitivity**
- **For proper demonstration of BE usually we need baseline correction of data**
- **Special population (Postmenopausal women?)**

Problem issue 4

Similar BE approach for non-oral dosage forms

- **Suppositories – how to reduce variability and prevent bowel movements after dosing**
- **Transdermal delivery system – requirements similar to MRF, must assess adherence to skin, irritation and sensitaztion etc., EMEA recommends replicate design**
- **Subcutaneus or intramuscular depot formulations – must cover the entire absorption period**

Problem issue 5

Locally Acting Drugs – corticosteroid nasal spray, inhalers for treatment of asthma, topicals as antibiotics, corticosteroids, drugs acting in the gut

- **Typical BE approach is usually not scientifically sound for locally acting drugs! Regulatory agencies may still accept BE assessment based on PK alternative methodologies still under discussion**
- **Pharmacodynamic or clinical endpoint studies are required for most locally acting medicinal products**

Problem issue 5

Medicinal products with non-linear PK – recommendations from the guidance

- **Use strength with the largest sensitivity to identify differences in formulation**
- **Steady state study may be required**
- **Fed study ?? Different interpretation of MS agencies**

Problem issue 6

Highly variable medicinal product

Single dose intra-subject CV > 30% for AUC

Replicate study design,

sample size determination

CONCLUSIONS

Main concerns:

- **Optimise standartisation of studies**
- **Invest in Bioanalysis**
- **Consider multiple dose designs**
- **Consider widening of the acceptance range**
- **Consider PD parameters**
- **Discuss with regulatory agencies whenever nonstandard approaches are used**

GCP/GLP Assessment

- **Unlogical protocol – too many protocol violations, insufficient explanations**
- **Missing documentation (validation report, demographic tables etc.)**
- **Data too clean (too smooth curves, very low intra-subject variability)**
- **Too many drop outs**

What to do in case of doubt?

- **Scientific advice from agencies**
- **Wider BE program to respond to all requirements**
- **Follow the guidelines**
- **You are responsible but discuss with CA**

THANK YOU !