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EUROPEAN GENERIC MEDICINES ASSOCIATION

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Assessing the Impact of Current Trends in Bioequivalance Requirements and their Impact on the Generic Medicines Industry

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Susana Almeida
Medical Department
Grupo Tecnimede, Portugal

Affiliations

- EGA Bioequivalence Working Group (co-chair)
- Medical Department, Farmoz, Grupo Tecnimede, Portugal
- Dept. Pharmacology, Therapeutics and Toxicology, Hospital de la Santa Creu i Sant Pau, Universidad Autònoma de Barcelona, Spain

Agenda

- Guidance on Bioequivalence in Europe
- 2006 Q&A
- Open topics
- Conclusions

Bioequivalence (BE) guidance in Europe - Immediate Release

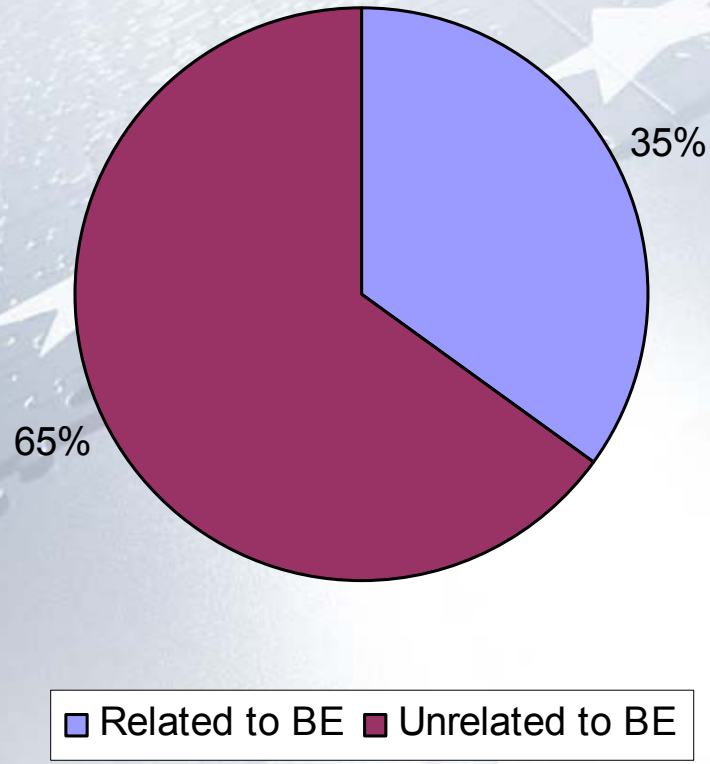
- Note For Guidance on the Investigation of Bioavailability and Bioequivalence, CPMP/EWP/QWP/1401/98 (2001)
- Q&A on the Bioavailability and Bioequivalence, EMEA/CHMP/EWP/40326/2006 (2006)
- Concept paper for an addendum to the BA/BE guidance: evaluation of the bioequivalence of highly variable drugs and drug products, EMEA/CHMP/EWP/147231/2006 (2006).

Update!

- 11/06/07 Recommendation on the need for revision of (CHMP)<Note for guidance on the investigation of bioavailability and bioequivalence> CPMP/EWP/QWP/1401/98
- 11/06/07 Concept paper on BCS-based Biowaiver

BE and referrals

- 29(1) Referrals to the CMD(h) (n=80)



Topics in the Q&A

- Widening of Cmax acceptance limits
- Interpretation of results
- Non-parametric approach
- Outliers
- Metabolite data: when to use
- Highly variable drugs and drug products
- Strengths to test
- Urinary data
- Food studies

Widening of Cmax interval: What the guidance said

"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 ...ons."

Therapeutic relevancy?
HVD?
Posology?
...?

Usually accepted limits: 80-125%

Wide intervals: example

- Bioequivalence studies:

The applicant has used the capsule for some early phase I and II studies, while phase III were conducted with the film-coated tablet. In order to show a reasonable degree of bioequivalence between these formulations, the applicant has provided relative bioavailability calculations of capsule versus film-coated tablet formulations. The resulting point estimate of AUC ratio is 108% with 90% CI confidence limits of 75-157%. For Cmax ratio, the point estimate is 95% with 90% confidence limits of 63-145%. While the confidence limits exceed the usual recommended limits, this is deemed justifiable in the present case. Ibandronate has a very low bioavailability and thus comes with inherent large variability that is reflected in the confidence intervals

Bonviva European Public Assessment Report. Scientific Discussion. Published 29/11/05

90%CIs

AUC: 75-157%

Cmax: 63-145%

BE accepted due to large variability

Q&A Answer (Section 2)

- **Widening to 75-133% acceptable if prospectively defined on the following basis:**
  - PK/PD data suggests that Cmax acceptance interval does not affect PD in a clinically significant way
  - Clinical safety/efficacy data should be specific for the compound to be studied and persuasive
  - Highly variable reference drug product (replicate design)

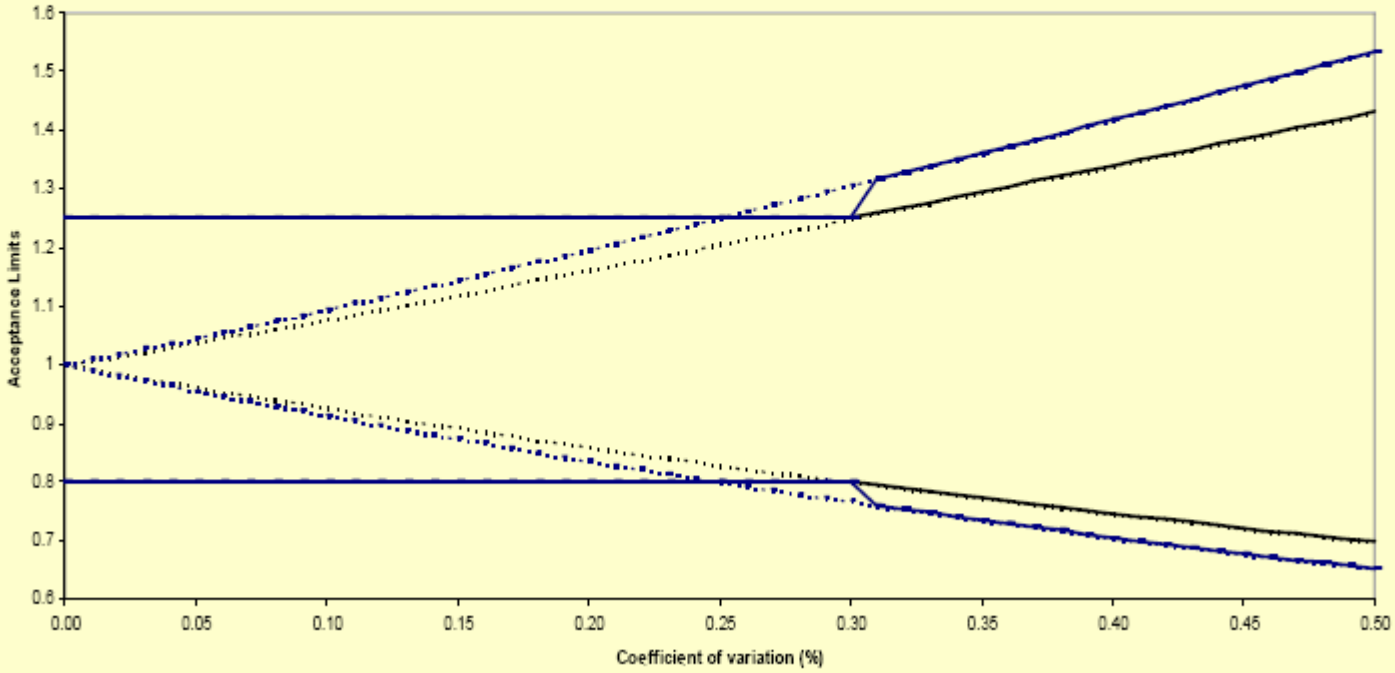
Highly variable drugs
Highly variable drug products

- **Within-subject variability is greater than 30% for the reference product (replicate design) - Q&A**
- **Several methods: scaled BE**
  - 90%CI acceptance interval is scaled as a function of the variability of the reference product

Scaled bioequivalence

Limits at CV = 30 or 25%

Acceptance Limits in original scale with ScABE versus within-subject variability



Garcia Arieta, 2006

- **Guidance document on high variability drugs**
  - Concept paper was adopted Apr 2006
  - Deadline for comments was Jul 2006
  - Release of draft guidance expected in 2007

Wider acceptance limits vs. sample size: example

Acceptance interval is an important component of a priori sample size calculation:
Alpha=0.05, power≈80%,CV=30%,T/R=95%

- **80-125%**
  n=40
- **75-133%**
  n=24
- **70-143%**
  n=16

Impact (widening)

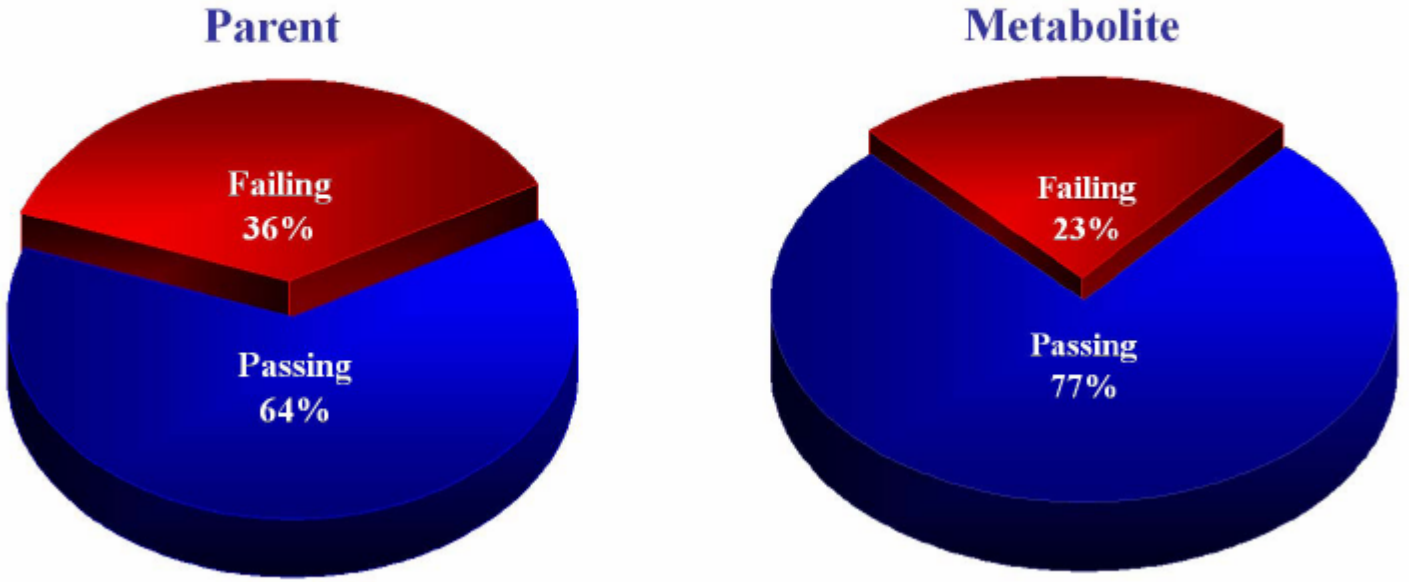
- **Less subjects required...**
  - Logistics of the trial (recruitment, clinic space, etc,)
  - Cost (clinical & analytical)
  - Ethics (main concern for regulators)

Metabolite data

- **BE should typically be based upon the parent compound**
- **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)

Data from a CRO (I)

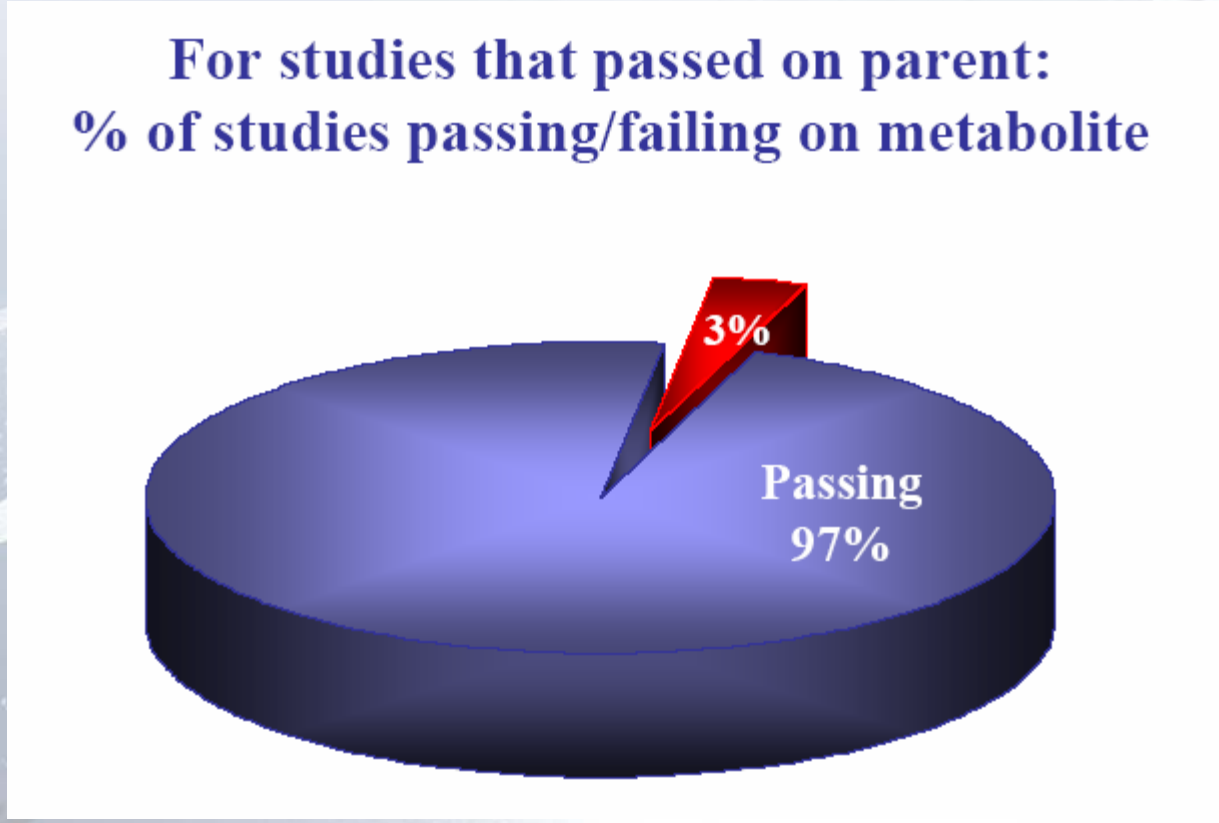
Studies where both parent and metabolite were measured: % of studies passing/failing for each analyte



(N=182)

Anapharm, Abolfathi, 2005

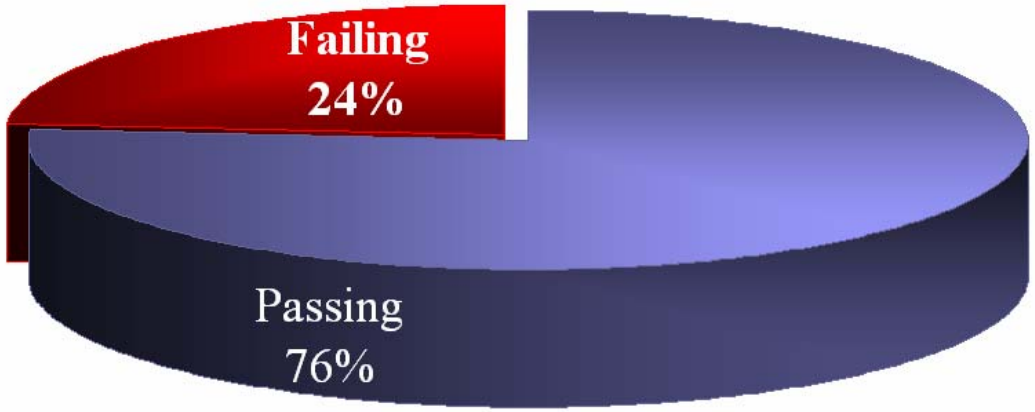
Data from a CRO (II)



Anapharm, Abolfathi, 2005

Data from a CRO (III)

For studies that passed on metabolite:
% of studies passing/failing on parent



Anapharm, Tanguay, 2006

Q&A Answer (Sections 6-7)

- Metabolite Cmax is not as sensitive to rate of absorption
- Concentrations are too low to detect based on state of the art technology

Impact

Analytical:

- Timelines
- Cost

Statistical:

- Type II error (not being able to show BE when formulations are BE) is typically 20% per each parameter: overall will be higher when more statistical analyses are performed

Strength to test?

5.4 Dose proportionality in immediate release oral dosage forms

If a new application concerns several strengths of the active substance a bioequivalence study investigati ed should be j he following c

- the pl
- the d ot the c vo prod
- the q
- the r se of pr o), the r
- the c itional stren

If a new strength (within the approved dose range) is applied for on the basis of an already approved medicinal product and all of the stated conditions hold then a bioequivalence study is not necessary.

Same manufacturing site, same process

+ dose proportionality (composition)

+ kinetics

= selected strength

Other strengths = similar dissolution profiles vs. BE strength

Pharmaceutical development

Proportional + same manufacturing site & process

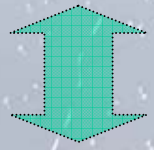
Linear PK

Strength A > B

Reference (Strength A)

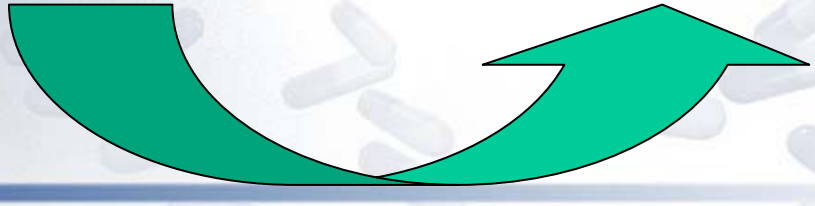
BE (Strength A)

Test (Strength A)



Biowaiver (Strength B vs A)

Test (Strength B)



One example of change in US-RLD strength:

Mirtazapine 15, 30 and 45 mg

First: 45 mg

Tolerability problems with 45 mg in the first trials

Current RLD: 15 mg

Extensive in vitro reference testing

- **Strengths**
  - Are the strengths proportional?

  Composition may be unknown but…

  … if weight is not proportional, they cannot be proportional
- **Dissolution**
  - Inter-batch variability (incl. inter-country)
  - Intra-batch variability (may affect waivers based on dissolution)

  = know what you are dealing with!

Reference product example: Azithromycin

- Spanish reference (15; 30; 37.5 mL)

15 mL: Add 10 mL of water

- Portuguese reference (15; 22.5; 30; 37.5 mL)

15 mL: Add 9 mL of water

- UK reference (15; 22.5; 30; 37.5 mg)

15 mL: Add 9 mL of water

Same reference?

Different markets: Relevancy of this?

Product/country	Batch no.	% Released in 45 min. (range)
Eulexin/Denmark	87G08 04	65 (62–70)
Eulexin/Denmark	87J20 09	54 (52–57)
Euflex/Canada	8XCPA 10	86 (85–88)
Eulexin/Denmark	88J28 14	77 (72–80)
Flucinome/Switzerland	88D27 05	94 (93–95)
Pugerel/Germany	89K09 10	51 (48–52)
Euflex/Canada	0XCPA 11	47 (44–51)
Euflex/Canada	0XCPA 12	47 (44–50)
Euflex/Canada	1XCPA 16	65 (62–72)
Flucinome/Switzerland	91A08 02	68 (63–73)
Drogenil/United Kingdom	92K04 17	66 (62–74)
Eulexin/Denmark	92I07 13	63 (61–64)
Eulexin/Finland	92K05 18	67 (63–73)
Pugerel/Germany	92L14 21	56 (54–59)
Drogenil/United Kingdom	93J22 21	62 (61–63)
Euflex/Canada	3XCPA 07	61 (59–63)
Flucinome/Switzerland	93A27 01	57 (53–62)
Flucinome/Switzerland	93B25 04	62 (61–64)
Flucinome/Switzerland	93C10 05	55 (64–65)
Eulexin/Italy	9	66 (63–69)
Flucinome/Switzerland	93F08 11	65 (63–67)
Flucinome/Switzerland	93I10 19	70 (67–74)
Pugerel/Germany	93I10 19	70 (67–72)
Eulexin/Italy	21	73 (72–75)
Eulexin/Italy	28	73 (69–80)

Flutamide

- **IVIVC**
  - AUCt metabolite correlates with % dissolved @ 45 min
- **Dissolution testing of several references**

Posti et al. Eur J Pharm Biopharm. 49(2000)-35-9

Posti et al. Eur J Pharm Biopharm. 49(2000)-35-9

The pharmaceutical examinations suggest that original flutamide 250 mg tablets of the same outer appearance and the same general pharmaceutical properties are distributed globally. However, marked batch-to-batch variability in the in vitro dissolution performance of the tablets was evident, irrespective of the marketplace. The results hence also suggest differences between batches in their relative bioavailability and, most probably, clinical safety and efficacy.

Base… acturer aimi… n with the c… lem so far n… elect a batch of the reference prod… as may be concluded from the experimental … ented in this report, shows marked batch-to-batch v… ility and, as may be further concluded, is suggested to b… non-bioequivalent within the brand itself! This kind of a rarely occurring situation may present a problem to the generic manufacturer aiming to show bioequivalence of its product with the original reference, and also to the regulatory authorities.

Non-bioquivalent reference batches?!

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Referral due to reference

- Sertraline 50 and 100 mg
- RMS: UK
- CMSs: AT, BE, CZ, DE, DK, EL, ES, FI, FR, HU, IE, IT, NL, NO, PL, PT, SE
- Problem: Bioequivalence for tablets shown against tablets; reference product available in Europe in different dosage forms.

The applicant had submitted the justification that in accordance with the guidance notes for the Investigation of Bioavailability and Bio-equivalence (CPMP/EWP/QWP/1401/98) any product is considered essentially similar to the reference product when it satisfies the criteria of the same qualitative and quantitative composition in terms of the active substance and having the same pharmaceutical form. Differences in the excipients for the tablets and capsules were not expected to cause any significant differences in efficacy or safety and dissolution data were provided to support similar bioavailability of the test and reference products. The company asserted that article 10.2(b) of the amended directive 2001/83/EC allows various oral immediate release dosage forms, such as tablets and capsules to be considered to be the 'same pharmaceutical form'.

The view of the CMD(h) was that this has to be substantiated for each pharmaceutical form.

The CMD(h) was of the opinion that it was the task of the Applicant to demonstrate bioequivalence against the relevant RMP, if there are different pharmaceutical forms available in different Member States and agreed that authorisation of the medicinal product could represent a serious public health concern in the CMS. In this case the RMP was available in alternative dosage forms.

Outcome

- Applicant made a commitment to submit results of <u>further bioequivalence study</u> against the test product against the capsule version on the RMP in a further application

= impact on the project timelines = impact on time to market and development cost

Watch out for

- Dosage forms
- New strengths
- Which countries?

Conclusions

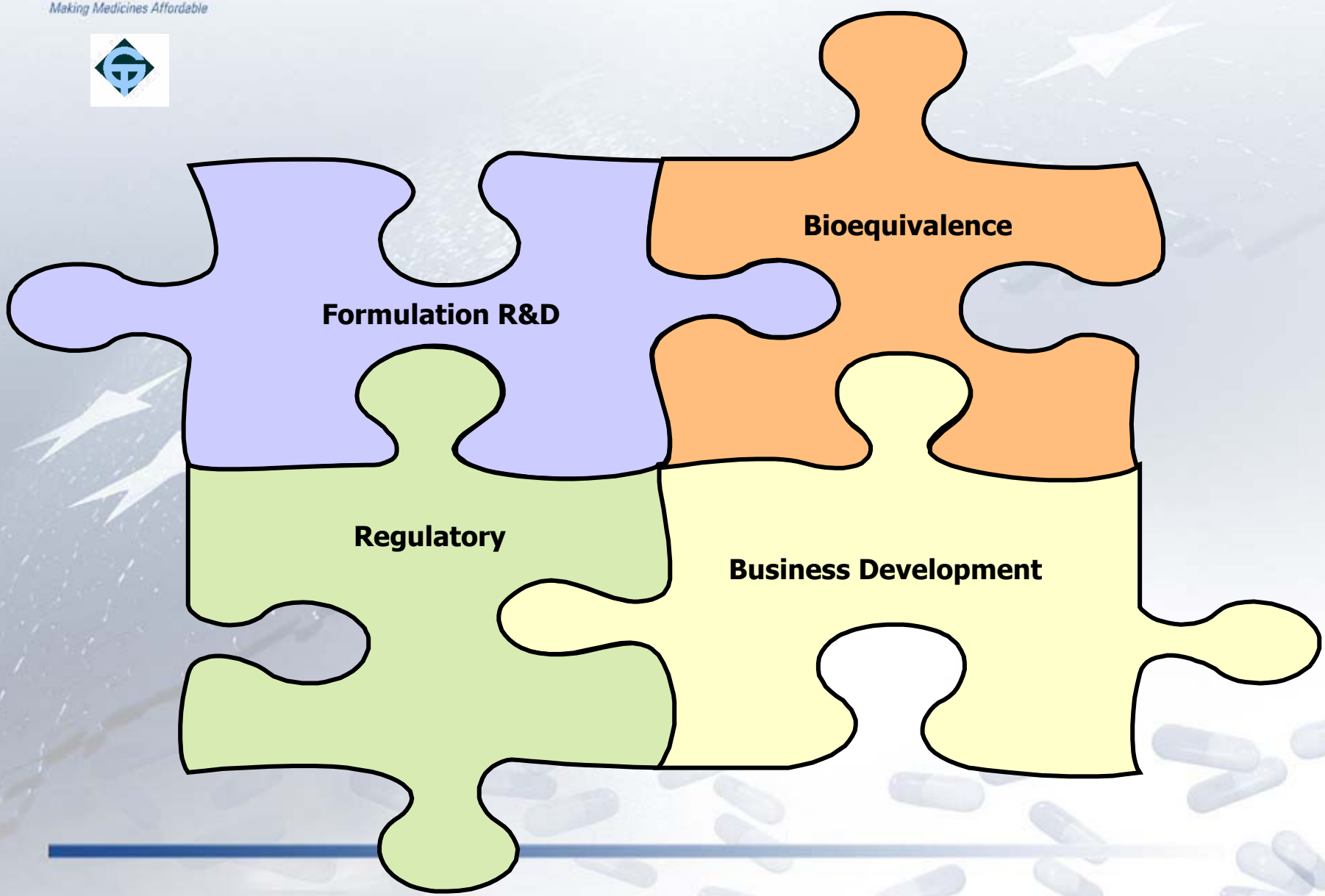
- Q&A focuses on some controversial topics in the NfG
- HVD/HVDP: guidance to be expected soon
- Still some unclear points that should be clarified... BE Note for Guidance will be revised
- **Business strategy is relevant to determine your BE strategy**

Tips

- **Before BE:**
  - Where do you plan to apply for a MA?
  - Plan your BE program according to the most complex scenario

- **At all times:**
  - Keep an eye on the regulatory/scientific environment: it keeps changing!!!

Integrated Strategy




In case of doubt?
Scientific advice from agencies
Harmonisation:
Required in order to avoid multiple BE programs!

Looking forward to seeing you in Lisbon!

1st EGA-Workshop on Bioequivalence:

Study Design, Working to GCP and Interpreting the Guidelines -

The Keys to a Successful Generic Application

Lisbon, Oct 24th 2007

Thanks to:

- Mary Smillie, Kevan Cassidy, the EGA's BE Working Group and EGA's team
- Augusto Filipe, Medical Director of Grupo Tecnimede, Portugal
- Zohreh Abolfathi, Assistant Director, Scientific and Regulatory Affairs, Anapharm, Canada

- & to the audience

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