Application of Guideline on clinical development of fixed combination medicinal products (EMA/CHMP/158268/2017) in real life:

Different indications – different requirements, strength biowaivers

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Disclaimer

DISCLAIMER

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Application of EMA/CHMP/158268/2017 in real life

Plan of the presentation

- About Polpharma
- Postulates of new Guideline
- Has paradigm really changed?
  - Generic company perspective
  - Regulator's perspective
- Cornerstone of 'relevant contribution'
- Possible indications:
  - Initial treatment: low dose / standard dose?
  - Add-on: non-responders to one mono treatment or all possibilities?
  - Substitution: the most complicated indication to receive?
- Bonus: strength biowaivers for fixed-dose combinations

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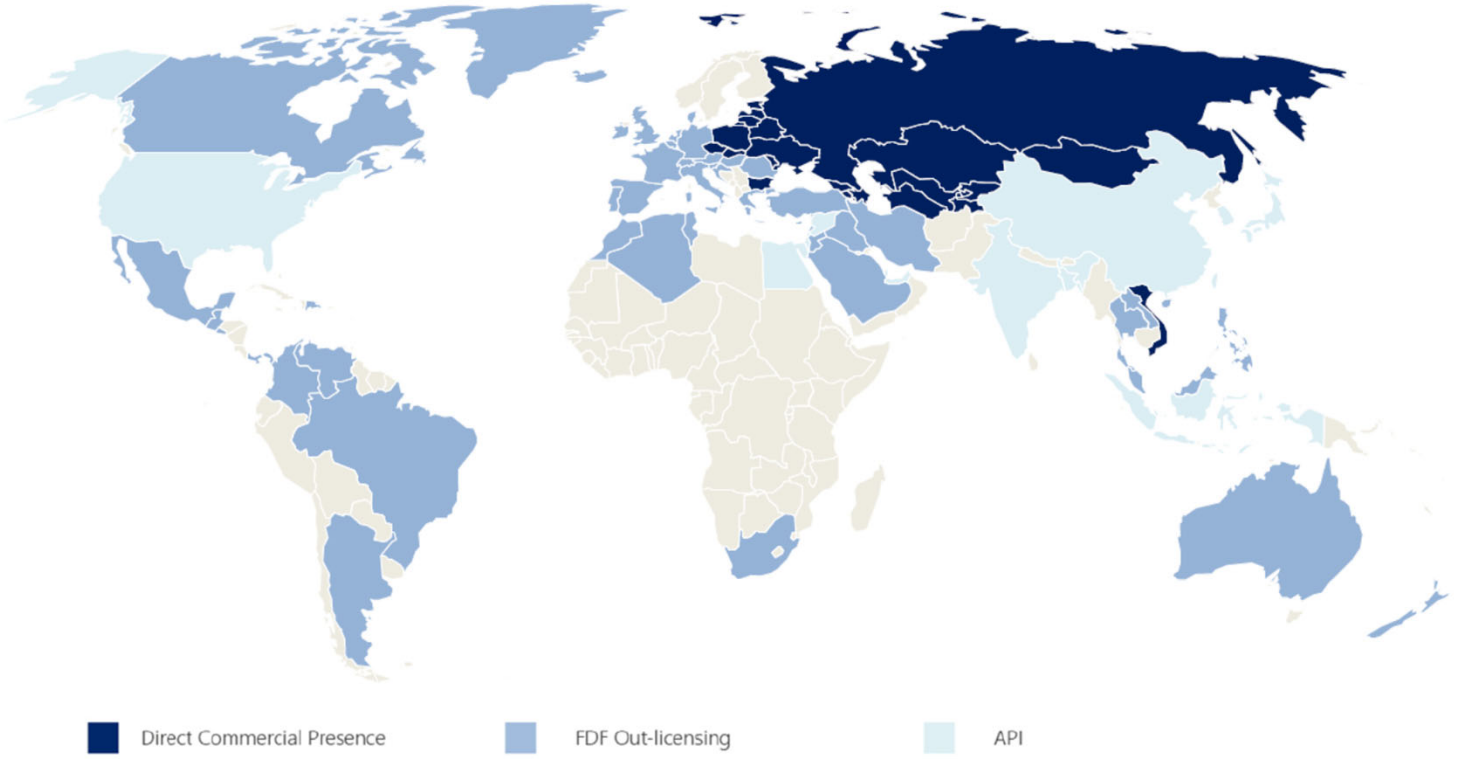
Introduction: Company profile

- **Polpharma** is a generic company specialized in the development of medicinal products as well as active substances.
- Polpharma's headquarters are located in Poland with more than 7,000 employees around the world.



Fixed Dose Combinations from Generic Company Perspective

- Generic products is our profession
- Small innovations within mostly ‘generic’ scope = ‘value added medicines’
- Combining of old/well-known molecules
  - Combination is plausible based on clinical practice and therapeutic guidelines
  - Some evidence of superior efficacy due to improvement of compliance
  - Some scarce published evidence (if available)
  - Co-prescriptions data
  - Bioequivalence study comparing FDC vs. co-administration of monoproducts
  - DDI study (not always)
  - Submission to obtain ‘substitution’ indication
- New combined therapy with generic price tag!

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New Guideline postulated 4 mandatory criteria:

- Pharmacological and medical ***rationale*** for the combination
  - Therapeutic guidelines already available
  - Co-prescription information easily available
- ***Evidence base for relevant contribution*** of each active substance
  - None of the above; indirect evidence not counts!
- ***Evidence base of positive benefit-risk*** in the indication sought
  - None of the above; indirect evidence not counts!
- Demonstration that available ***evidence is relevant to FDC***
  - Bioequivalence study(-ies) vs. co-administered monoproducts

You Shall Not Pass!!!

The Lord of the Rings, 2001

Side notes

Our journey with FDCs

- We studied this GL and connected GLs
- We consulted it with Agencies
- Briefing document had 100 pages and roughly 50 pages of attachments…
- The more we dive in, the more questions arise…
- Now we came to Prague… Is it legal after all?

Elon smokes...

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Has paradigm really changed?

- It depends on which Member State you are going to apply…
  - Some states still approve completely new combinations based on theoretical benefits based on some expert justification and successful bioequivalence
  - You can hear opinion that nothing has really changed. Applicant was always expected to demonstrate relevant contribution and positive benefit/risk benefit for desired indication. It was well-known to big companies from their original developments, but now have been written in a more precise way. No paradigm change at all.
  - Well, there are also opinions that requirements are much more formalized now. Straightforward interpretation of the guideline leads to conclusion that clinical programs for some well known ‘original’ combinations will not be sufficient for approval.
  - In my opinion, new ‘generic’ combinations of well-known substances are practically killed now, and I will explain why…

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Cornerstone of ‘relevant contribution’

- Logic behind this requirement is simple: two (or more) substances co-administered should provide superior clinical effect due to either additive effect or potentiation.
  - Simple example from essential hypertension: different classes of blood pressure lowering agents have synergy potential due to different action points which results in decrease of blood pressure. ACEI (ARB) + CCB or ACEI + diuretic
    - While combination may decrease pressure better, will risk of cardiovascular events be decreased using a combination?
    - What about safety? Famous double RAAS blockade case.
- Only direct evidence is acceptable to claim relevant contribution
- All strengths should be tested!?
- Special exploratory factorial study is advised to make such conclusion

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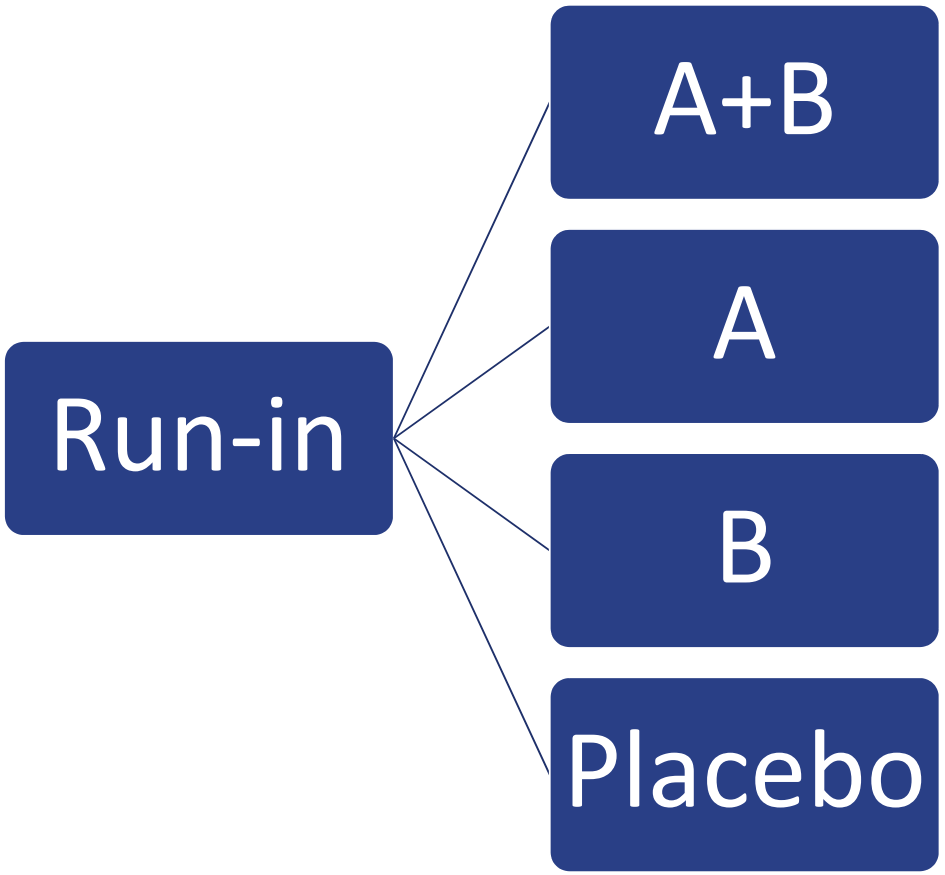
Factorial/exploratory studies



- Strictly exploratory trial to demonstrate PD interaction, cannot be pivotal
- Justifies only the relevant contribution
- More strengths combinations – more arms in the study
  - Higher combo strengths expected to demonstrate superiority vs. same strength mono and lower strength combo
  - It can be a really huge study
- Placebo arm is expected
  - Needed to demonstrate sensitivity
- Easiest pharmacodynamic/clinical endpoint to be selected as primary
- Superiority vs. Monotherapy required
  - At least statistically significant
- Superiority vs. Placebo required
  - Clinically and statistically significant
- Total length of the study depends on slowest acting active substance

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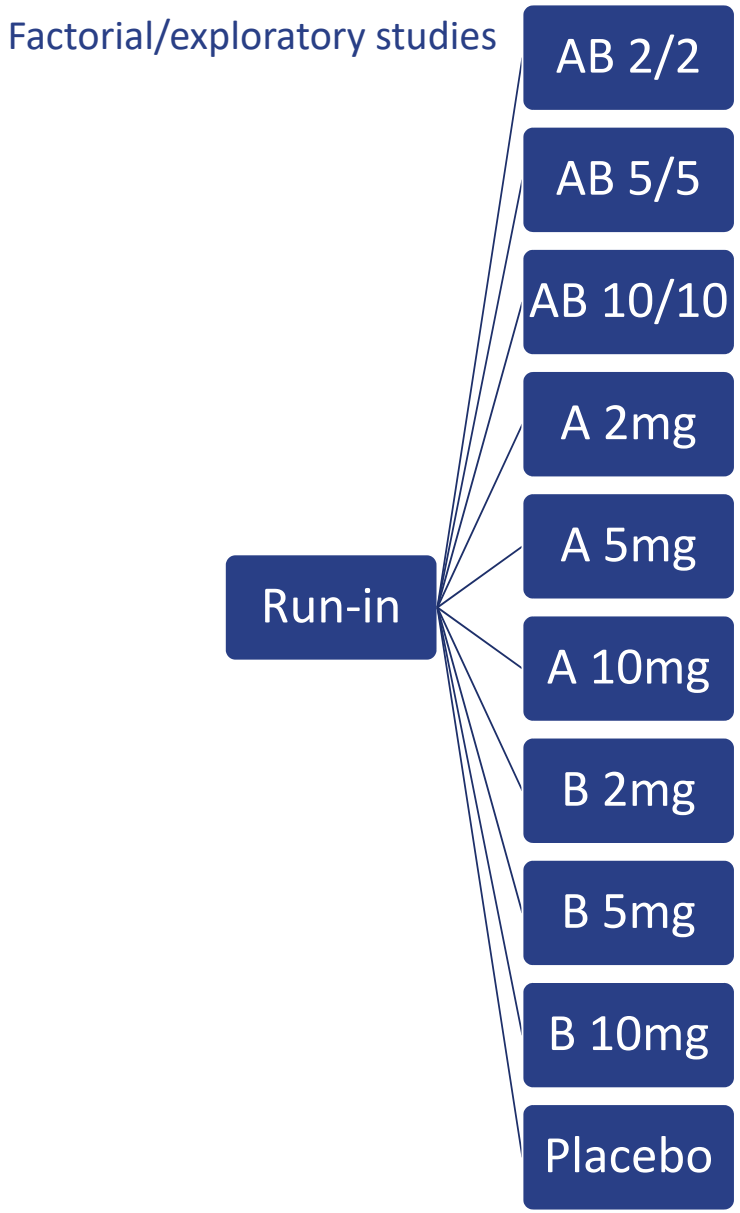

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Add-on indication (second / third line therapy): GL text

- Combination product is intended for use in patients who do not respond satisfactory to existing therapy at optimal dose(s) for sufficiently long period of time with one (or more of the) active substance(s) in the FDC
- PK studies: DDI directly required
  - PK of the individual substances should be well-understood
  - What about comparative BA of FDC vs. monoproducts?
  - Population PK analyses to address specific populations
- Factorial PD endpoints studies with all dose permutations can waive dose steps in pivotal study
- Pivotal: RCT to demonstrate superiority of FDC in non-responders population vs. individual active substances
- Study should be based on clinical practice

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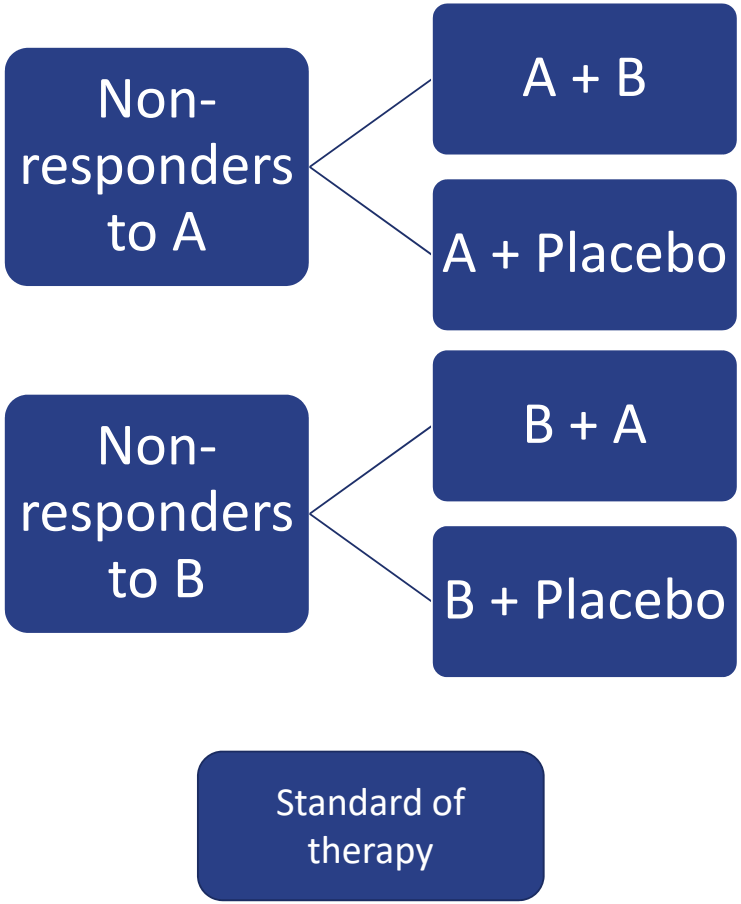
Add-on indication: application



- Applicable only for moderate and higher doses (we switch from 'optimal' dose of mono)
- Designed based on factorial study data
  - Otherwise: one study = one strength for one indication
- Pure placebo arm is not required and not ethical
  - Some conditions (oncology, infections) will not allow use of ineffective monotherapy with placebo
- Endpoints suggested (hypertension):
  - Statistically significant and clinically relevant reduction of the SBP AND DBP + statistically significant reduction in responders rate
  - SAMPLE SIZE ESTIMATION???

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Initial treatment indication: GL text

- Patient is to be immediately treated with a combination of medicinal products, instead of the stepwise addition of the active substances in the fixed combination medicinal product based on the individual patient response
- Advantages of starting the therapy with two (or more) active substances at the same time outweigh its disadvantages
- Exploratory factorial PK/PD trial with placebo arm is strongly advised
- Pivotal trial expected to demonstrate superior efficacy (or faster achievement of response) or improved safety vs. mono-products
- Preferred by therapeutic guidelines now!

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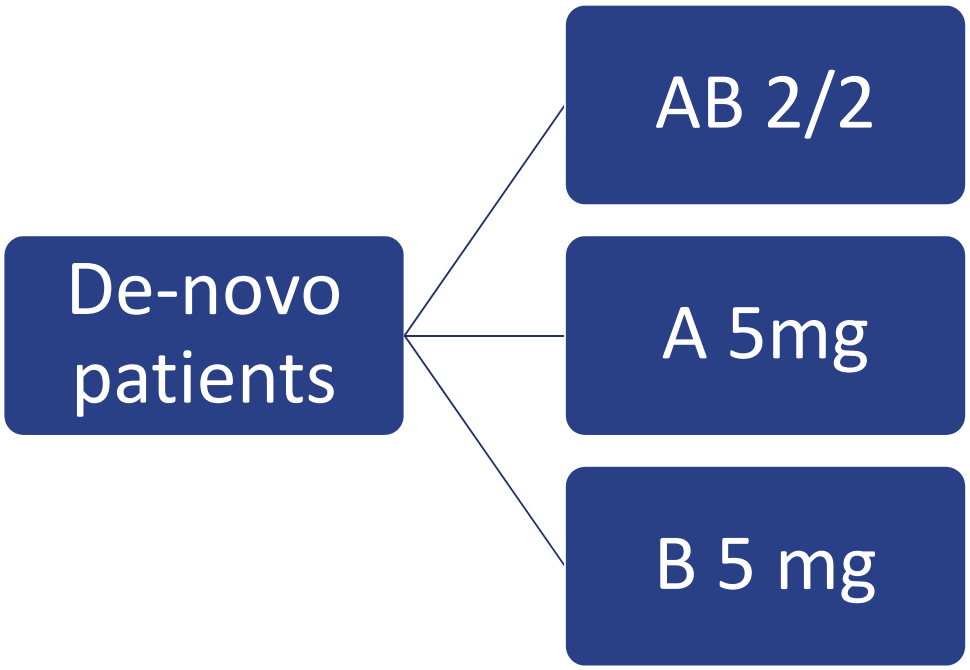
Initial treatment indication: subtherapeutic doses



- Designed based on factorial study data
  - Subtherapeutic doses of mono products should still be statistically superior to placebo in factorial trial
- Subtherapeutic combination should demonstrate superiority or at least non-inferiority to lowest approved doses of mono products
- More titration steps – more complicated study
- Safety benefits demonstration – potential killer for this scenario
  - Safety endpoints much more demanding to sample size, we can easily get thousands of patients from statistician

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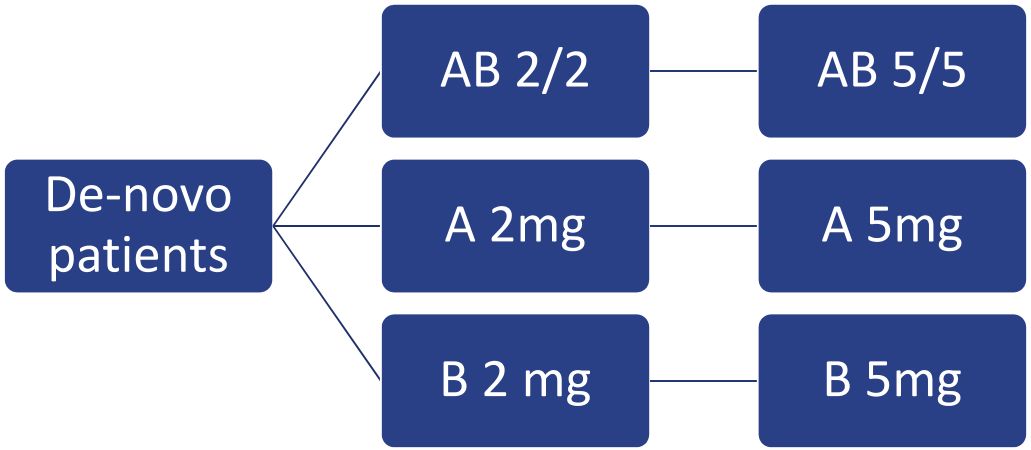
Initial treatment indication: therapeutic doses



- Risk of adverse events related to improved efficacy should be consulted prior to application of this approach
  - Essential hypertension: is it safe to start treatment using standard lowest doses of the mono products?
  - Do we have safety evidence behind new therapeutic requirements?
- Designed based on factorial study data
- Should test titration steps
- More titration steps – more complicated trial
- Safety benefits demonstration – potential killer for this scenario

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Substitution treatment indication: GL text

- Patients are already responding good to a coadministration of 2 or more mono products; we replace 2 units with 1
  - Still need to provide evidence of relevant contribution
  - And positive risk-benefit balance of the combination in the particular indication is positive
- We substitute either initial treatment, or add-on treatment, or both
  - Depends on evidence body available for co-administration of two (or more) active substances
- Evidence of absence of significant drug-drug interaction
  - Absence of evidence is not an evidence of absence
  - If direct DDI data not published – may be asked to perform such study
- Bioequivalence versus co-administration

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Substitution treatment indication: case of Ramipril+Amlodipine

- There is no 'Reference' product registered based on full dossier
- Products already registered use PK study(-ies) as pivotal, rest based on literature (excluding some post-marketing trials)
  - Miranda, 2008: 18-week RCT on 200+ de-novo (washed-out) patients comparing R+A vs. A+placebo (no separate Ramipril mono arm), starting dose was 5 mg, dose escalated to 10 mg ramipril and 10/10mg A+R. (Peer-reviewed journal)
    - Study provides evidence to support initial treatment indication: combination was statistically significantly superior in SBP reduction vs. amlodipine in PP population.
    - Ramipril mono arm is missing, will combination be superior vs. Ramipril 5mg up-titrated to 10 mg?
  - Duprez, 2008: Aliskiren vs. Ramipril alone or in combination with HCTZ and Amlodipine in elderly (>65 y.o.) systolic hypertension patients (untreated or washed-out)
    - After 36 weeks R+A+HCTZ was non-inferior to Aliskiren+A+HCTZ.
    - Theoretically, non-responders to Ramipril+HCTZ benefit from addition of Amlodipine
  - WU Hong-jie, 2010: uncontrolled hospital study, low level of evidence
  - China practical medicine, 2009: uncontrolled hospital study, same as above
  - Lovic, 2012 (conference abstract)
    - Combination demonstrated superiority in BP reduction vs. ramipril monotherapy.
    - Type of study? Population of patients?
- What do we substitute?

Chip 'n' Dale: Resque Rangers, Dysney 1989-1990

Strength biowaivers for FDC

Bonus track: application to fixed-dose combinations

Composition criteria for biowaiver between strengths

a) the pharmaceutical products are manufactured by the same manufacturing process,

b) the qualitative composition of the different strengths is the same,

c) the composition of the strengths are quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance(s) is the same for all strengths (for immediate release products coating components, capsule shell, colour agents and flavours are not required to follow this rule),

If there is some deviation from quantitatively proportional composition, condition c is still considered fulfilled if condition i) and ii) ori) and iii) below apply to the strength used in the bioequivalence study and the strength(s) for which a waiver is considered

i. the amount of the active substance(s) is less than 5 % of the tablet core weight, the weight of the capsule content

ii. the amounts of the different core excipients or capsule content are the same for the concerned strengths and only the amount of active substance is changed

iii. the amount of a filler is changed to account for the change in amount of active substance. The amounts of other core excipients or capsule content should be the same for the concerned strengths

Fixed combinations

The conditions regarding proportional composition should be fulfilled for all active substances of fixed combinations. When considering the amount of each active substance in a fixed combination the other active substance(s) can be considered as excipients. In the case of bilayer tablets, each layer may be considered independently.

What can be used for justification?

- **Ratios**
  - Summary of the discussions held at the 3rd EGA symposium on Bioequivalence June 2010 | London
  - Deviations from the guideline recommendations on proportionality / pseudo-proportionality criteria for biowaiver of other strengths could be considered possible in justified cases. This requires case by case assessment of the supportive data provided by the applicant as it is difficult to define upfront general criteria.
- **Bracketing**
  - We can have different kinds of extremes (extreme formulation)
  - And Extreme dissolution

Strength biowaivers for FDC

Substitution treatment indication: case of Ramipril+Amlodipine

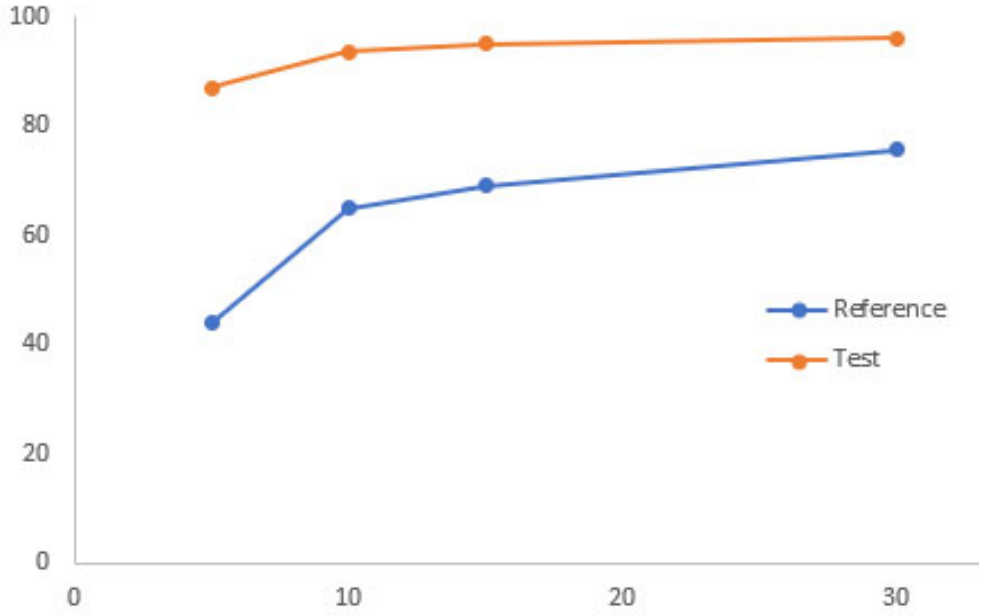
VS.		ABC 5/100/7.5 Lot:X			ABC 5/100/7.5 Lot:Y			ABC 2.5/100/15 Lot:X			ABC 2.5/100/15 Lot:Y		
ABC 5/100/15		A	B	C	A	B	C	A	B	C	A	B	C
	0.1HCl												
	4.5												
	6.8												
	4.5+SLS												

Strength biowaivers for FDC

Bonus track: application to fixed-dose combinations

GL requirements:

Dissolution appropriate in vitro dissolution data should confirm the adequacy of waiving additional in vivo bioequivalence testing (see section 4.2).



- Highly soluble active substance, paddles apparatus, 50 RPM, 900 mL
- No bioequivalence risk with such profiles: AUC: 105%, Cmax: 107
- Dissolution may be predicted by serious mathematical equations, which remains rather a crystal ball for us now

Even if justified, what are other hurdles?

- Biowaiver justification?
- Testing of first production batches for all strengths
- Can we apply the same justification for such non-similarities?
- Release specification for production may be nasty as well
- If these questions cannot be answered upfront, there may be hurdles in selection of BIO batch

Thank you!