Overview of International Regulatory Guidelines

Dr Natasha Rafter
Cardiovascular Combination Pharmacotherapy Global Summit
Melbourne, May 2014
Disclosure Statement of Financial Interest

I, Natasha Rafter DO NOT have a financial interest/arrangement or affiliation with any healthcare related companies that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation.
Background

• A fixed dose combination (FDC) is a combination of 2 or more actives in a fixed ratio of doses (WHO Annex 5)
• 1960s widespread use of FDCs – Rx and OTC
• FDA policy 1971- prove efficacy
• Today combination therapy is emerging as the standard of care in certain disease settings (FDA)
Common themes

- Public health need
- Rational combination
- Contribution - justify each active/dose
- Use of scientific literature
EMA

• Article 10b Directive 2001/83/EC
– combination of active substances which are authorised medicinal products

“it shall not be necessary to provide scientific references relating to each individual active substance”
EMA

- Guideline on clinical development of fixed combination medicinal products (under revision CHMP/EWP/240/95)
- Q&A document on the clinical development of fixed combinations of drugs belonging to different therapeutic classes in the field of cardiovascular treatment and prevention (CHMP/EWP/191583/2005)
- Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **)
- Guideline on clinical investigation of medicinal products in the treatment of hypertension (EMA/238/1995/ Rev.4 DRAFT)
- Guideline on clinical investigation of medicinal products in the treatment of lipid disorders (EMA/CHMP/718840/2012)
Q&A FDCs of Different Therapeutic Classes for CVD

• Substitution indication
  – wide therapeutic experience, established B:R ratio
  – not for first line therapy
  – 3 scenarios for PK/PD - dose interval/timing

• Wider indication
  – new clinical development – factorial study (dose selection), outcome studies
Clinical Development of FDCs
(under revision)

- Justification - improvement of B:R, simplification (substitution indication)
- PK – FDC vs free combination
- Corresponds closely to existing simultaneous use - bibliographic data (reduce clinical trials, facilitate dose selection)
- Therapeutic trials
  - first line (FDC vs individual substances/placebo/reference)
  - second line (FDC vs optimal monotherapy)
- Safety – abridged database if wide experience in claimed indication at proposed dose (or 6/12)
FDA

• 21CFR300.50
  – Efficacy, safety, contribution, medical need

  “each component makes a contribution to the claimed effects and the dosage of each component...is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy...”
FDA

• 505(j)
  – Generics
  – BE – no clinical trials required

• 505(b)(2)
  – New combination product with previously approved ingredients
  – Public domain studies
WHO

• Annex 5 Guidelines for registration of fixed-dose combination medicinal products
  – Less well developed nations
    • Cost
    • Improved reliability of supply (simplified distribution)
    • More available - better patient adherence
### Scenario Studies Required

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Studies Required</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Existing FDC</td>
<td>BE – FDC vs existing FDC</td>
</tr>
<tr>
<td>2. Same actives/same doses as an established regime of single entity products</td>
<td>BE – FDC vs free combination</td>
</tr>
</tbody>
</table>
| 3. Established actives not previously used in combination or different dosage regimen | Preclinical – not required if all actives extensively used in same combination for a long period  
Clinical – if can’t use monotherapy in trials then use historical clinical data plus bridging PK data and preclinical pharm/tox.  
Safety data > 6/12 – include existing experience |
| 4. Contains a new entity                                                 | Full dossier                                                                     |
## India

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>STUDIES REQUIRED</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. One ingredient not approved in India</td>
<td>NCE, except if FDC marketed in another country or in India but new indication/dose/ratio</td>
</tr>
<tr>
<td>II. All ingredients approved in India</td>
<td>BE (FDC vs free combination) plus literature</td>
</tr>
<tr>
<td>A. similar FDC marketed in another country</td>
<td></td>
</tr>
<tr>
<td>B. not marketed anywhere but ingredients used concomitantly for same indication at same dose</td>
<td></td>
</tr>
<tr>
<td>III. FDC marketed in India but new ratio/dosage form</td>
<td>Literature ± BE</td>
</tr>
<tr>
<td>IV. Subsequent approvals (generics)</td>
<td>BE</td>
</tr>
</tbody>
</table>
Examples - indications

• Amlodipine/valsartan/HCTZ
  – EMA/Australia: *Treatment of essential hypertension as substitution therapy in adult patients whose blood pressure is adequately controlled on the combination of amlodipine, valsartan and HCT, taken either as three single-component formulations or as a dual-component and a single-component formulation.*
  – Switzerland: *Treatment of essential hypertension... indicated in patients whose blood pressure is not adequately controlled by dual therapy.*
  – FDA: *Treatment of hypertension. Not indicated for initial therapy.*

• Amlodipine/atorvastatin
  – FDA/Australia: *indicated in patients for whom treatment with both amlodipine and atorvastatin is appropriate.*
Examples - trials

• Amlodipine/atorvastatin
  – 3 way BE
  – Factorial, n=1660, 15 arms, placebo, 8 weeks
  – Approved in US, Australia

• Amlodipine/valsartan/HCTZ
  – Efficacy, n=2271, FDC vs dual therapy, 8 weeks
  – BE - FDC vs free combination, PK - target population
  – Approved in US/Australia/EU

• Polycap
  – n=2053, FDC vs 8 groups, 12 weeks
  – PK - 5 arm (monotherapy), healthy volunteers
  – Approved in India
Other conditions

• HIV
  – FDA HIV FDC guideline – no new clinical evidence, factorial study not ethical, lists drugs and provides literature references

• WHO Essential Medicines List
  – encourages FDCs for antiretrovirals, antimalarials, antituberculosis drugs
Challenges

- Paradigms research / regulators
- Public health research / pharmaceutical trials
- Generic manufacturers capacity
- Funding
- BE - local references, 5 way study
- Components not indicated for CVD prevention
- Perception chronic disease need
- Substitution indication does not meet clinical need
Questions for the panel

• Substitution indication does not meet clinical need
  – Data required for step up treatment for partially treated?
  – Data required for CVD prevention indication?
• Regulatory requirements for multiple dose versions?