Rationale and Strategies for Development of Oral Fixed-Dose Combination Drugs

2016 KSPST/AAPS Joint Symposium: Development of Fixed-Dose Combination: Current Experience and Future Perspectives

November 17, 2016
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Fixed-Dose Combination Drug Product

• FDC: prevalent for the disease management in almost all therapeutic areas

• FDC drug therapies: widely accepted due to providing several clinical benefits
  - Enhanced therapeutic efficacy and safety
  - Patient compliance and convenience
  - Reduced treatment cost to patients
  - Increased patient adherence to the combination therapies
  - Eventually improved disease treatment and management

• Significant contributions to improving public health
  - Treating communicable and life-threatening diseases (HIV/AIDS, malaria, tuberculosis HBV/HCV and CV diseases)
  - Enhanced patient care and compliance with lower costs
Fixed-Dose Combination Drug Product

From many different perspectives
- A promising approach to achieving clinical benefits and business advantages

• From a clinical perspective
  - Offer enhanced therapeutic efficacy and safety profiles with improved patient adherence and reduced development of drug resistance

• From a patient perspective
  - Improved convenience/compliance and reduced dosing unit burden (simplified dosing regimen)
  - Cost savings: cost-effective than individual single drugs
  - Elderly patients: long-term multiple medications to treat age related chronic complex diseases and their co-morbidities

• From an industrial perspective
  - Opportunities to maximize the value of single drug products, to sustain their product’s life, and ultimately to extend market exclusivity with a resultant increase in sales and profits
Development of FDC Drug Products

- Increased over the past two decades: considerable portion of new drug products; many FDC blockbusters in the global pharmaceutical market

- Developed mainly for:
  - Substituting for free combinations being frequently used
  - Treating two closely related diseases
  - Unmet needs of patients insufficiently controlled by monotherapies

- Oral FDC drug products: highly advantageous and technologically advanced in the treatment of various diseases (cancer, tuberculosis, HIV/AIDS, HBV/HCV, hypertension, dyslipidemia, diabetes, pain and other CV diseases)

Source: <www.pharmacircle.com>
## Selected Examples of Oral FDC Drug Products Recently Approved

<table>
<thead>
<tr>
<th>Indication</th>
<th>Combination drugs</th>
<th>Therapeutic action</th>
<th>Brand (Company)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>Amlodipine besylate/Perindopril arginine</td>
<td>CCB/ACE inhibitor</td>
<td>Prestalia® (Symplmed)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Nebivolol/valsartan</td>
<td>Beta blocker/ARB</td>
<td>Byvalson® (Allergan)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>Ezetimibe/Atorvastatin</td>
<td>Cholesterol absorption inhibitor/HMG-CoA reductase inhibitor</td>
<td>Liptruzet® (Merck)</td>
</tr>
<tr>
<td>Heat Failure</td>
<td>Valsartan/Sacubitril</td>
<td>ARB/Nepriysin inhibitor</td>
<td>Entresto® (Novartis)</td>
</tr>
<tr>
<td>2nd prevention of CVDs</td>
<td>Aspirin/Omeprazole</td>
<td>Antiplatelet/PPI</td>
<td>Yosprala® (Aralez)</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>Metformin HCl/Canagliflozin</td>
<td>Biguanide/SGL T2 inhibitor</td>
<td>Invokamet® (J &amp; J)</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>Metformin HCl/Empagliflozin</td>
<td>Biguanide/SGL T2 inhibitor</td>
<td>Synjardy® (Boehringer Ingelheim/Eli Lilly)</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>Empagliflozin/Linagliptin</td>
<td>SGL T2 inhibitor/DPP-4 inhibitor</td>
<td>Glyxambi® (Boehringer Ingelheim/Eli Lilly)</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>Sofosbuvir/Ledipasvir</td>
<td>Hepatitis C virus NS5A inhibitor/NS5B polymerase inhibitor</td>
<td>Harvoni® (Gilead)</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>Raltegravir/Lamivudine</td>
<td>HIV-1 integrase inhibitor/NRTI</td>
<td>Dutrebis® (Merck)</td>
</tr>
<tr>
<td>Obesity</td>
<td>Bupropion HCl/Naltrixone HCl</td>
<td>NDRI/Opioid receptor antagonist</td>
<td>Contrave® (Takeda)</td>
</tr>
<tr>
<td>Dementia</td>
<td>Donepezil HCl/Memantine HCl</td>
<td>Acetylcholinesterase inhibitor/NMDA receptor antagonist</td>
<td>Namzaric® (Allergan/Adamas)</td>
</tr>
<tr>
<td>Nausea &amp; vomiting</td>
<td>Netupitant/Palonosetron HCl</td>
<td>NK1R antagonist/5-HT3 receptor antagonist</td>
<td>Akynzeo® (Roche/Helsinn)</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>Ivacaftor/Lumacaftor</td>
<td>CFTR stabilizer/CFTR potentiator</td>
<td>Orkambi® (Vertex)</td>
</tr>
</tbody>
</table>
Development of FDC Drug Products

Growth trend is likely to continue: growing market size

- Long-term concurrent therapies employing oral FDC drugs: recognized to be effective for the patient populations with multiple chronic diseases that are readily affecting to each other

- Great increase trend in elderly patient population who in most cases need long-term concurrent drug therapies

- Growing high risk patient population: early combination drug therapies to proactively reduce multi-morbidity, mortality and organ damages → investigating potential early drug combinations

- Advances in screening and prediction methodologies (systems pharmacology/therapeutics): rationale for drug combinations, rationality of active component selection

Source: <www.pharmacircle.com>
Basic Regulatory Requirements for FDC

WHO

“New FDC drugs are regarded as new drugs in their own right. They are acceptable only when the dosage of each ingredient meets the requirements of a defined population group, and the combination has a proven advantage over single compounds administered separately in terms of therapeutic effect, safety or compliance. They should not be treated as generic versions of single-component products.”

US FDA

“Two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effects and the dosage of each component (amount, frequency, duration) is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling for the drug.”

Source: WHO Tech Rep Ser No. 929; FDA 21CFR 300.50
Disease treatment with single drugs acting on specific targets: maybe suboptimal due to showing insufficient therapeutic efficacy and safety, undesired side or adverse effects, short duration of action and drug resistance

- Single target vs. multiple target treatment
- Single-target vs. multi-target drugs in drug actions: other functions (drug network of interactions: principal target vs. off-targets)
- Pharmacokinetic characteristics and pharmacogenetic variations

Cardiovascular diseases and complications: end result of complex pathophysiology from metabolic diseases, exhibiting multiple pathogenesis → require multiple target drug therapies

Peng L et al., BMC Syst Biol 8:141 (2014)
Unmet Needs Not Fulfilled by Monotherapies

• Unmet needs for a target patient population
  - Unique characteristics in terms of age, physical state of functions, pathophysiological conditions, co-existing diseases, differentiated drug response and resistance, pharmacogenetics and genetic polymorphism affecting PK and PD (patient centricity) → patient focused selection of active components, dose strength, dosage form and dosing regimen

• Unmet needs analysis
  - Systematic literature review, survey of clinical practitioners, prescription pattern database

Source: McKinsey Global Institute analysis
Potential Risks in FDC Product Development

Potential risks and drawbacks
- Unimproved or suboptimal therapeutic effectiveness
- Exposure of patients to unnecessary drugs
- Unexpected or serious adverse (side) effects and safety issues
- Multiple unbeneﬁcial drug-drug & drug-excipients interactions
- Unacceptable dosage regimen: reduced patient adherence

Additional disadvantages of FDC drug products
- Lack of dosing ﬂexibility
- Misidentiﬁcation of causes for undesirable effects
- Instability of FDC products

Main reasons
❖ Lack of rationale for drug combinations: irrational justification
   - Deﬁnition of target patient population and indications (unmet needs)
   - Rational selection of active components and their doses
   - Understanding of potential therapeutic beneﬁts, drug-drug interactions and combination effects
❖ Unappropriate FDC product development strategies
Rationale for Drug Combination

- Rationale for drug combinations can be well established only when potential benefits are theoretically based on valid therapeutic principles and later proven by clinical evidences.

Source: The Therapeutic Research Institute
## Rationale for Drug Combination

### Therapeutic Benefits or Advantages: individually or combinedly

| Addition or potentiation of therapeutic activity | - An enhanced efficacy with a similar safety/tolerability profile, or a similar efficacy with an improved safety/tolerability profile (more effective than the higher doses of component drugs with similar side/adverse effects, or as effective as the higher doses of component drugs with lower side/adverse effects)  
- Examples: antihypertensive + antihypertensive or diuretic; antidiabetic + antidiabetic |
| Improvement in symptomatic and pharmacokinetic profile | - Increase in the pharmacological intensity and duration of one component drug produced through changes in its PK caused by other components not previously approved for the relevant indications: antiretroviral agent(s) + booster agent  
- Improvement in the safety profile of one drug achieved by diminishing its dose-related side/adverse effects based on some interactions with other components: opioid agonist + antagonist |
| Improvement of patient compliance | Better therapeutic outcomes, without benefits of enhanced efficacy/safety, anticipated by the improved patient compliance obtained from simplified therapies. |
Rationale for Drug Combination

Pharmacodynamic and Pharmacokinetic Interactions

- Enhanced efficacy and safety: results from the sum of independent actions of individual components and/or their beneficial PD and PK interactions
- The PD and PK interactions: mutually related and multiply involved in the therapeutic effects of drug combinations at the same time

| PD interactions | - Effects of one drug at its action site modified by another drug: classified into acting on same targets and acting on different targets in same or different biological pathway
  - Examples: exenatide decreasing rosiglitazone-associated myocardial infarction; emodin complementing the inactivation of protein kinase B by celecoxib |
|-----------------|--------------------------------------------------------------------------------|
| PK interactions | - Absorption, distribution, metabolism and excretion behaviors of one drug altered by another drug: classified in terms of regulation of drug transport and distribution, and interaction of drug metabolism and elimination
  - Examples: probenecid inhibiting the renal tubular secretion of ciprofloxacin to prolong its plasma retaining time; anamorelin elevating the absorption rate of zolmitriptan to improve the migraine treatment |

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### Rationale for Drug Combination

#### Combination Effects: individually or combinedly

<table>
<thead>
<tr>
<th>Effect Type</th>
<th>Description</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Additive or synergistic effect</strong></td>
<td>- Affecting the same PD end-point (marker/surrogate) with different pharmacological mechanisms and contributing to additive or synergistic effects on reduction of disease severity/risk&lt;br&gt;- Examples: antihypertensive, antiviral and antidiabetic combinations; exenatide decreasing rosiglitazone-associated myocardial infarction; statin + ezetimibe; aspirin + dipyridamole</td>
<td></td>
</tr>
<tr>
<td><strong>Complementary effect</strong></td>
<td>- Affecting different PD end-points and contributing to additive or synergistic effects on reduction of disease risk/complications&lt;br&gt;- Examples: antihypertensive or antidiabetic + statin</td>
<td></td>
</tr>
<tr>
<td><strong>Cooperative effect</strong></td>
<td>- One of component drugs with different pharmacological mechanisms affecting the activity of the other, leading to enhancement of effectiveness, reduction of adverse effects, drug resistance and/or abuse potential&lt;br&gt;- Examples: amoxicillin + clavulanic acid; aspirin + omeprazole; diphenoxylate + atropine</td>
<td></td>
</tr>
<tr>
<td><strong>Convenience effect</strong></td>
<td>- Convenience and improved patient compliance by simplifying drug therapies and reducing dosage unit burden&lt;br&gt;- Examples: multiple combinations of antihypertensive, anticholesterol and antidiabetic antiplatelet drugs</td>
<td></td>
</tr>
</tbody>
</table>
# Rationale for Drug Combination

<table>
<thead>
<tr>
<th>Different targets of related pathways that regulate the same target</th>
<th>Candesartan-cilexetil (angiotensin AT&lt;sub&gt;1&lt;/sub&gt; receptor antagonist&lt;sup&gt;200&lt;/sup&gt;)</th>
<th>Ramipril (ACE inhibitor&lt;sup&gt;201&lt;/sup&gt;, reduces angiotensin II formation&lt;sup&gt;202&lt;/sup&gt;)</th>
<th>Synergistically reduces systolic BP&lt;sup&gt;203&lt;/sup&gt;</th>
<th>Dose–response curve shifted 6.6-fold leftwards compared with hypothetical additive curve</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enhanced drug distribution or localization</td>
<td>Cerivastatin (cholesterol-lowering: HMG-CoA reductase inhibitor)</td>
<td>Gemfibrozil (inhibits CYP2C8-mediated metabolism of statins, inhibits OATP2-mediated uptake of cerivastatin&lt;sup&gt;227&lt;/sup&gt;)</td>
<td>Increases plasma concentration of statins by inhibiting their metabolism and uptake&lt;sup&gt;227–229&lt;/sup&gt;</td>
<td>Enhances level of drug in plasma by metabolism reduction and uptake inhibition</td>
</tr>
<tr>
<td>Drug metabolism</td>
<td>Warfarin (anticoagulant and antithrombotic, affects coagulation proteins that act sequentially to produce thrombin, metabolized by CYP3A4&lt;sup&gt;234&lt;/sup&gt;)</td>
<td>Quinidine (stimulates CYP3A4-mediated metabolism of warfarin&lt;sup&gt;235&lt;/sup&gt;)</td>
<td>Reduces anticoagulant effect of warfarin by stimulating its metabolism&lt;sup&gt;235&lt;/sup&gt;</td>
<td>Enhances metabolism of active drug into inactive metabolite</td>
</tr>
</tbody>
</table>

Rational Selection of Component Drugs

• Selection of a combination of therapeutic targets: based on the identified pathogenesis, novel pathways and pathophysiological characteristics of targeted diseases

• Selection of potential active components
  - Based on action mechanisms and principles underling therapeutic benefits of drug combinations
  - Using screening and computational prediction methodologies, and PBPK-IVIVE linked modeling/simulation of drug combinations
  - Therapeutically contributing to the desired combination effects and efficacious drug-drug interactions
  - Avoiding the drugs showing unbeneficial drug-drug interactions
  - Ratio of benefit to risk: at least as good as that of each drugs
  - Established drugs with well-documented development data and information
  - Drugs having similar PK behaviors: favorable

• Effects of active components on the PD end points of the combination
  - To evidence the contributions of each components
  - To establish the therapeutic efficacy and safety of the combination
Systems Pharmacology/Therapeutics

- Effect of a drug: outcome of the network of interactions
- High-throughput screening and computational prediction methodologies using target network analysis and genomics/bioinformatics systems
- PBPK-IVIVE linked modeling and simulation

Target-enzyme interaction networks between drug combinations
<Park J et al., IBC 5:1 (2013)>

Target Network Analysis: DrugComboRanker for prioritizing disease specific drug combinations
<Huang L et al., Bioinformatics 30:228 (2014)>


Strategy to define combination mechanisms of drug action

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Proposed Fixed-Dose Combinations

• Unmet needs analysis based on clinical database for IHD treatment
• Theoretical rationale for the drug combinations
• Studies on beneficial effects of the drug combinations in animal disease models
• Pharmacokinetic interaction studies: PBPK-IVIVE linked modeling and simulation, PK studies in human subjects and in rats
• FDC formulation development
# Development of Oral FDC Drug Products

## Challenges and Considerations

<table>
<thead>
<tr>
<th>Challenges and Considerations</th>
<th>Strategies</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Multiple dose ratios and doses of active components: number of different dose strength FDC products influencing formulation design, manufacturability, product performance evaluation and clinical studies</td>
<td>• Alternative dosage form/formulation or minimal changes in formulation</td>
</tr>
<tr>
<td>• Different physicochemical and biopharmaceutical properties of active components</td>
<td>• Dose-proportionate FDC: bio-waivers for the lower dose strengths after establishing the BE for the highest dose strength FDC</td>
</tr>
<tr>
<td>• Different PK behaviors of active components</td>
<td>• Careful consideration of physicochemical properties of active components for formulation design and process development</td>
</tr>
<tr>
<td></td>
<td>• Identifying BCS class of active components: use of formulation design and technologies for controlled drug release, absorption and solubilization enhancement</td>
</tr>
</tbody>
</table>
## Development of Oral FDC Drug Products

<table>
<thead>
<tr>
<th>Challenges and Considerations</th>
<th>Strategies</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Possibility of physicochemical drug-drug and drug-excipients incompatibility: leading to</td>
<td>• At the 1st step of formulation design, testing physicochemical compatibility: avoiding incompatible</td>
</tr>
<tr>
<td>physicochemical instability of FDC product, loss of BA and safety issues</td>
<td>excipients and impurity generation</td>
</tr>
<tr>
<td>• Different drug release (or dissolution) patterns, PK profiles and dosing regimen of individual</td>
<td>• Drug-drug incompatibility: formulating FDC products to minimize the physiochemical interactions by</td>
</tr>
<tr>
<td>drug products</td>
<td>keeping the active components separated.</td>
</tr>
<tr>
<td>• Formulation design to address PK/PD interactions and to carry single dosage regimen of FDC</td>
<td>• FDC product with a single dosing regimen unified for the component drugs</td>
</tr>
<tr>
<td>product</td>
<td>• Formulation platform for managing component drugs in a single dosage form to be separately released</td>
</tr>
<tr>
<td>• Availability or development of combination drug delivery and formulation technologies applicable</td>
<td>at proper rate and duration with individual drug delivery programs</td>
</tr>
<tr>
<td>to FDC product</td>
<td>--------------------------------------------------------------------------------------------------------</td>
</tr>
</tbody>
</table>
# Development of Oral FDC Drug Products

<table>
<thead>
<tr>
<th>Challenges and Considerations</th>
<th>Strategies</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Bioequivalence (BE) and clinical study issues: drug-drug interactions in FDC product and possible food effects on component drugs</td>
<td>• Establishing BE as a favorable approach to assess the equivalency between a FDC and co-administered individual single products</td>
</tr>
<tr>
<td>• Development and validation of analytical and testing methods for FDC product</td>
<td>• Some drugs may have positive or negative food effects: differentiating</td>
</tr>
<tr>
<td>• Possibility of Increased dosage bulk volume (or weight) of FDC product</td>
<td>• Potential BE failure risk to be considered in selecting FDC formulation approach: higher for BCS Class IV drugs than for other BCS classes of drugs</td>
</tr>
<tr>
<td>• Increase in quality attributes and process factors of FDC product</td>
<td>• Patient-acceptable volume of dosage form: minimized/optimized</td>
</tr>
<tr>
<td>• Process-ability and manufacturability of FDC formulation</td>
<td>• Implementation of “Quality by Design” approach</td>
</tr>
<tr>
<td>• Physicochemical stability issues and increase in stability testing items (impurity profiling)</td>
<td>• Securing long-term stability</td>
</tr>
</tbody>
</table>
Formulation Development of Oral FDC Products

Decision Tree for Formulation Design

Physicochemical drug-drug and drug-excipients compatibility; Similarity of drug release profiles; Drug loading

- FDC for two or more drugs
  - Physicochemical compatibility
    - Yes
      - Similar Dissolution Profile
        - Yes
          - Monolithic systems
        - No
          - No
            - Bilayer/multilayer tablets
            - Multiparticulates
            - Active coating
    - No
      - Very low drug loading

Formulation Development of Oral FDC Products

Dosage Form Design and Formulation Technologies

• Monolithic systems
  - Component drugs: compatible to each other, similar dissolution profiles
  - Monolithic FDC tablet: prepared using a conventional tablet press

• Bi-layer/Multi-layer tablets
  - One of the best options to circumvent physicochemical incompatibilities of APIs or to achieve the different drug release profiles of each drug in a single dosage unit by physical separation
  - Severe incompatible drugs: the buffer layer inserted between the two layers to prevent direct contact of two APIs
  - Polypill: multi-layer tablets of multiple component drugs

Moodley K et al., Int J Mol Sci 13:18 (2012)
Formulation Development of Oral FDC Products

Dosage Form Design and Formulation Technologies

• Multi-layer coated tablets/capsules (Active film-coating approach)
  - Core tablet/capsule: IR active coating on IR or ER single/multi-layer active core
  - two different drug release profiles with minimizing chemical interactions

Formulation Development of Oral FDC Products

Dosage Form Design and Formulation Technologies

• Multiparticulate systems
  - Pellets (beads) prepared by extrusion/spheronization or layering the drug solution or suspension onto sugar pellets and/or granules compressed into tablets or encapsulated into capsules
  - Coated pellets applicable to oral modified release

Source: Internet Scientific Publications: http://ispub.com/IJTWM/8/1/4313
https://pharmaceuticalresearch.wordpress.com/2012/07/05/sodas-spheroidal-oral-drug-absorption-system

Source: www.laboratory-journal.com
Formulation Development of Oral FDC Products

Dosage Form Design and Formulation Technologies

- **Hot-melt co-extrusion approach**
  - Multi-layered extrudate by extruding simultaneous hot-melt of two or more materials through the same die

- **Polycap**
  - Pellets, granules, tablets, mini-tablets, soft/hard capsules filled in capsules
Questions

Thank you for your kind attention!

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