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**COMBINATION PRODUCT OVERVIEW: FIXED DOSAGE**

## Combination Product Overview: Fixed Dosage

In today's competitive pharmaceutical environment, building & maintaining market share is paramount. With dwindling pipelines, limited resources, & expiring patents, now, more than ever, combination products are being considered in drug development portfolios. However, regulatory hurdles, physician acceptance, and market strategy, are just a few considerations that one should address. This brief overview will cover specifics regarding fixed dosage combinations (FDC's), and will hopefully give your company a better understanding to the challenges ahead. Patients have already seen the benefit of combination products in areas such as oncology, cardiology, neurological, metabolic disorders, respiratory, HIV, as well as several other areas. Whether you are considering an solid, liquid, or topical, you need to be well informed in areas such as the current market, the regulatory environment, and formulation development challenges. In terms of the industry, revenues for combination products, as a whole, are expected to reach \$11.4 billion by 2010<sup>1</sup>. Further, some sources estimate that 30% of new products under development are combination products<sup>2</sup>. With technology advances (nanotechnology, genomics, molecular diagnostics, tissue engineering etc.), combination products may offer us a promising future.

### **Past/Present/Future (excerpts from John Ansel, Combination Product Conference June 2009)**

- Successful combinations in 2008 - YAZ®, Atripla®, Kaletra®, Infarix/Pediatrix®, Augmentin®, Vitorin®, Caduet®
- New in 2009: Novartis Exforge ® (amlodipine/valsartan), a replacement for patent expired Lotrel®. Also Exforge HCT ® (triple active). This complex, fixed combination makes it increasingly difficult for a new compound to enter into the combination market.
- Common areas of focus: anti-infectives, CNS, cardiovascular, diabetes, contraceptives, HIV, and respiratory
- Future products include:
  - Targin ® - CNS/Pain control pain and counteract constipation side effect
  - Arthritis – Anti-inflammatory and gastric ulcer treatment
  - Cardiovascular – Lipid lowering and statin combination
  - Asthma – many products addressing chronic obstructive pulmonary disease (COPD)
- Untapped Opportunity for Generic - Branded Products:
- Match existing drugs to serious unmet needs in different therapeutic categories



## Why develop fixed-dose combinations (FDC)? (courtesy Tony Ellery, Combination Product Conference June 2009)

1. Lower side effects
2. Synergistic efficacy
3. New indications/new patient populations
4. Move to first-line treatment over prescription numbers/charges/costs
5. Higher convenience = higher compliance
6. New IP, rebrand, or new market exclusivity more of the components currently protected by patent?

**Corporate Goals:** What is your end goal? Do you have an upcoming patent expiring on a mono-therapy dosage and wish to protect your market share before or after genericization? Perhaps there is a potential to increase your current market share of one or more of the components currently protected by patent?

Lets review some common strategies that companies follow for FDC's. Identify and focus on a strategy that best meets your goals above.

1. Protect existing branded business by switching patients to a FDC.
2. Compete by increasing overall brand market share and taking away rival brand share
3. Expand brand into new patient segments not currently reached by your current drug class

## Success factors for FDCs

1. Formulation development challenges: A variety of issues potentially exist when combining multiple actives. It is not as simple as combining two or more actives in a tablet press or capsule. Understanding the chemistry, mechanism of action of each component, as well as drug substance pre-formulation characteristics, are paramount. An experienced formulator can make all the difference in helping you obtain / protect current IP, as well as make duplication by competitors extremely difficult. Speed to market is important, as well as holding off competitors. Below are just a few formulation considerations:



1.
  - a. Incompatibility
  - b. Release profile differences
  - c. Particle size
  - d. Delivery challenges
  - e. Regulatory requirements-  
[www.emea.europa.eu/pdfs/human/ewp/024095en.pdf](http://www.emea.europa.eu/pdfs/human/ewp/024095en.pdf)
2. Patent & Exclusivity
3. Pricing & Reimbursement
4. Physician resistance

## Patent Feasibility

Obtaining patents is not as simple as submitting a concept that appears unique. Your product must be innovative and show functionality. This is easier said, than done. Typically, patents are granted under the following criteria:

1. Must be “novel” i.e. not publicly
2. Must be “inventive”, i.e. not obvious over what was already publicly known (“prior art”)
3. Must be “utilizable”, i.e. has functionality It should be noted that the “obviousness” hurdle is getting higher each year. If you have an idea or unique concept, chances are, so has somebody else. It is a good idea to research whether someone has gone down that road prior. The more successful combination products typically focus on unmet medical needs. To strengthen your patent, build innovation into your formulation. Generic companies are getting better at circumventing formulation patents. CoreRx Inc. 6101 Johns Road Tampa Florida 33634 ph: 813.514.9399 [www.corerxpharma.com](http://www.corerxpharma.com) If you are hoping to extend your current product patent duration, particularly in the USA, at least one of the active ingredients must have not been previously approved previously by the FDA.

## Market Exclusivity

- USA submissions: Combination products qualify for five (5) year NCE exclusivity if ALL actives are new chemical entities. Otherwise a three (3) year label exclusivity will be issued.
- EU submissions: Combination products qualify for Data exclusivity for 8-11 years, especially if it is a new indication



## Pricing & Reimbursement

1. Premium pricing above mono-therapy is becoming more difficult.
2. Increased unit sales should be the primary goal.
3. Reimbursement is not typically an issue if combination product is not premium priced.
4. Reimbursement at premium pricing will only hold if there is a clear beneficial outcome.

## Physician Considerations

1. Many physicians prefer to select relative dosing of combination components on an individual patient
2. Any need to titrate the drug dose can add complications.
3. Identifying source of side effects can be difficult.
4. Patience may potentially be exposed to drugs they do not really need.
5. Conceptually, medication management & compliance should improve with patients. However, little evidence exists regarding compliance improvement.
6. Physician's increasingly see combination products as industry's

## Information Sources

There is a variety of information available via the FDA, organized groups, consultants, and development contractors. Becoming educated is the first step to deciding whether a combination product (FDC) is a fit for you.

- FDA <http://www.fda.gov/CombinationProducts/default.htm>
- Combination Product Coalition <http://www.combinationproducts.com>
- Combination Product Guidance to Industry & FDA  
[http://combinationproducts.com/images/CPC\\_ClinTrialFAQFINAL.pdf](http://combinationproducts.com/images/CPC_ClinTrialFAQFINAL.pdf)
- LinkedIn. If you currently use this forum, you can join the Combination Product Group to open up discussions and/or learn industry experiences.

Excerpts from Cambridge Healthtech Institute (CHI) Combination Product Symposium, June 2009. Presenters: John Ansell Consultancy, John Maki, President and CEO, Vicus Therapeutics, LLC, Tony Ellery, Ellery Pharmaceutical Consulting, Also contributions from Brian McMillan, Director Formulation Development, CoreRx Inc.





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