The Pharmaco-economics of Combination Therapies: A Study of the Effects of Component and Market Factors on Combined Therapy Price

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ABSTRACT

For a growing number of indications, combination therapies are becoming increasingly common due in part to their superior efficacy, as compared to monotherapies. In fact, in the case of infectious diseases such as AIDS and tuberculosis, combination therapies are now the standard of care. With the emergence of drug-device combinations, genetic testing, and individualized medicine, this trend towards combination therapies is likely to continue to grow.

In this context the pricing of combination therapies is a critical component that needs to be understood by medical practitioners, payors and policy makers. There are three factors to consider in the pricing of combination therapies: the characteristics and structure of the market in which the combined product is sold, the absence or presence of market exclusivity, and the prices of the components of the combined product, when sold individually. When one or more of the components of the combined product has market exclusivity, additional factors such as exclusionary bundling, tying, and double marginalization may come into play.

In this thesis I discuss combination therapies, describe the factors that can affect the pricing of combination therapies, and then attempt to identify the relationships among component pricing, market forces, market exclusivity and the pricing of combination therapies.

To illustrate these relationships empirically, I will analyze data from a sample of unified combined drugs, a subset of combination therapies.

The results of this analysis are consistent with a hypothesis that, for combination drugs with a patented ingredient, the elimination of double marginalization by efficient transfer pricing and economic and exclusionary bundling, lowers the price of the unified combination drug relative to the price of its constituents.

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DEDICATION

To my wife Evelyn and our children Sofia and Sen:
For their love and support.

To my parents:
For all their sacrifices.

To my brother Shridhar and my sister Subitha:
For their moral support.

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Introduction

For a growing number of indications, combination therapies are becoming increasingly common[1] due in part to their superior efficacy, as compared to monotherapies. In fact, in the case of infectious diseases such as AIDS and tuberculosis, combination therapies are now the standard of care. With the emergence of drug-device combinations, genetic testing, and individualized medicine, this trend towards combination therapies is likely to continue to grow.

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In this thesis I discuss combination therapies, describe the factors that can affect the pricing of combination therapies, and then attempt to identify the relationships among component pricing, market forces (which will be defined), market exclusivity and the pricing of combination therapies.

To illustrate these relationships empirically, I will analyze data from a sample of unified combined drugs, a subset of combination therapies (which will be elaborated below).

Unified combination therapies

In this thesis, combination therapy refers to the usage of multiple products for a single treatment. For example, one tablet of aspirin and one tablet of Plavix is the standard of

[1] "Pharmaceutical Industry turns to drug combinations", The Brown University Psychopharmacology Update, The Brown University Press, 2004

care for patients who have undergone coronary stent implantation[2]– this would be an example of a combination therapy. Unified combination therapy refers to a physically bundled and inseparable delivery of multiple products. For instance, a single tablet with multiple active ingredients will be referred to as a unified combination drug. A combination therapy could be a combination of two or more drugs, a drug and a device, or a diagnosis and a therapeutic treatment. In the case of a combination of two drugs or a drug and a device, the products can be made inseparable thus creating a unified combination product.

Pharmaceutical and device companies have increasingly focused on unified combination products for a variety of reasons.[3] These reasons will be further explored for each of the different types of combinations.

Combination therapies: Drugs

Clinical benefits of combination drugs

Some combination drugs are more effective against infectious agents

The emergence of drug-resistant strains of infectious agents due to multiple drug-resistant (MDR) mutations has resulted in the use of a cocktail of antibiotics or antivirals in the treatment of infectious disease.[4] Adding a combination of antibiotics rapidly raises to astronomical values the number of cell divisions required by bacteria to attain resistance to the drug. The number of divisions required by tuberculosis to acquire resistance to one drug is empirically understood to be 10^6, while the number of divisions required for resistance to three drugs would be 10^{18} an exponentially larger number[4]. As a result, combinations are the preferred mode of treatment for AIDS, tuberculosis, malaria, and other infectious diseases that rapidly gain resistance to monotherapy.

Another use of a combination drug is the bundling of one component that may have no direct therapeutic effect, but aids the second component in achieving the result, a

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[2] Daniel M. Kolansky, Bruce D. Klugherz, Sean C. Curran, MD, Howard C. Herrmann, Kathleen Magness, Robert L. Wilensky, John W. Hirshfeld Jr., "Combination Therapy with Clopidogrel and Aspirin After Coronary Stenting", Catheterization and Cardiovascular Interventions, January 2000.
[3] "Pharmaceutical Industry turns to drug combinations", The Brown University Psychopharmacology Update, The Brown University Press, 2004
[4] Albert I Wertheimer, Alan Morrison ,"Combination Drugs: Innovation in Pharmacotherapy", Pharmacy & Therapeutics, January 2002, 27 (1) 44:49

phenomenon called potentiation. For example, clavulanate inhibits bacterial production of beta-lactamase – an enzyme that degrades amoxicillin. This restores the activity of amoxicillin against strains that have developed a gene encoding beta-lactamase. Similarly, carbidopa prevents the inactivation by the human body of levadopa, which is used to treat Parkinson's disease.[5] Combinations can also increase the therapeutic index, the ratio of the toxic dose to the therapeutic dose, by cancellation – where the adverse effects of one drug are cancelled by the activity of another component, for example a combination of a diuretic, which is hypokalemic, with an ACE-inhibitor, which is hyperkalemic.[5]

Combinations of drugs can have fewer side effects than a large dose of a single drug

The side effects of most drugs are generally related to the dosage of the drugs being used; dose-related adverse reactions – known as augmented reactions - are thought to be responsible for approximately 80% of adverse drug reactions (ADRs).[6] A combination of drugs may reduce the side effects by lowering the dose of each component drug below the threshold level that causes the side effects.

In some cases, while a combination of lower doses can result in fewer side effects, the therapeutic effect on the disease will still be additive, thereby treating the disease effectively with fewer side effects.

The most cited example of this effect is in the case of antihypertensive drugs, where combinations of diuretics, ACE inhibitors, and calcium channel blockers are used with greater efficacy and fewer side effects than a larger dose of any one agent alone.

In fact, in recent clinical trials for hypertension, results show that single drug therapy seldom achieves the desired blood pressure, while combination therapy is more likely to achieve the desired result.[7]

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[5] Albert I Wertheimer, Alan Morrison ,"Combination Drugs: Innovation in Pharmacotherapy", Pharmacy & Therapeutics, January 2002, 27 (1) 44:49
[6] "Adverse drug reactions", National Medicines Information Centre Magazine, 2002;8(3):1-4
[7] Some combination drugs can lower your pill bill", Harvard Heart Letter, June 2004:5

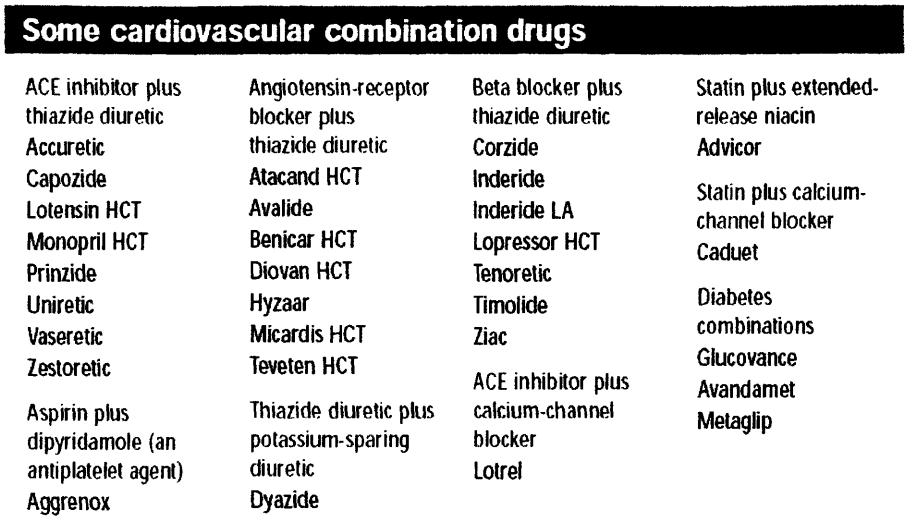

Figure 1: Cardiovascular Combination drugs from Combination Drugs: Innovation in Pharmacotherapy, Wertheimer and Morrison[8]

There are, however, other classes of drugs where this logic does not hold. For example, in the case of antiseizure medications, the side effects are often additive when combination treatments are used, leading to a larger number of side effects. This is presumably because the therapeutic dose of each of the component drugs is above the threshold level that causes these side effects.[9]

Unified combination drugs aid better compliance

Studies have shown that patients are more likely to comply with a regimen of fewer tablets or capsules per day.[10] Unified combination therapies also reduce fixed costs, including the cost of packaging, co-pays by the patient, and reduced number of prescriptions, making them more economical. Furthermore, forced joint consumption ensures that the patient cannot take only one agent of a combination therapy and thus reduces the chance of the infectious agents acquiring serial resistance to each of the components.

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[8] Albert I Wertheimer, Alan Morrison ,"Combination Drugs: Innovation in Pharmacotherapy", Pharmacy & Therapeutics, January 2002, 27 (1) 44:49

[9] HST Pharmacology lectures, Carl Rosow, Harvard Medical School, March 2006

[10] Haynes RB,"A critical review of the determinants of patient compliance with therapeutic regimens. Compliance with therapeutic regimens" In: Sackett DL, Haynes RB, Editors, *Compliance with therapeutic regimens*, Johns Hopkins University press, 1976 :26-39

This desire for increased compliance has spawned novel ways of combining drugs to increase compliance, including a 'polypill'– a pill with five drugs and one vitamin[11]. This polypill, if taken by all adults over 55, according to certain researchers, could potentially prevent 88% of all heart attacks and 80% of all strokes[11].

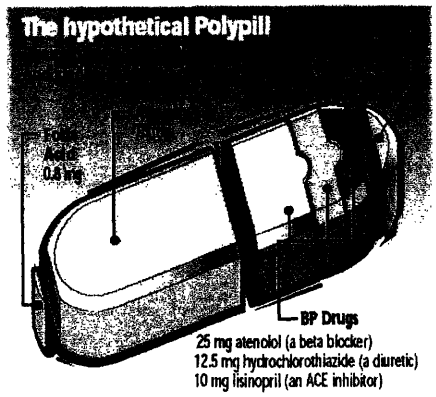

Figure 2: The Hypothetical Polypill from Harvard Health Letter, July 2004[11]

In half of all cases of eye infections, a combination of topical treatments is indicated. A combination, in this case, is virtually a requirement due to the difficulty in applying multiple products to the eye.[12]

Economic benefits of combination drugs

Unified combination drugs are often cheaper

Combination drugs are often less expensive than the sum of their constituents. Hence, when combination drugs are unified, they are often more economical. A patient could, for instance, save $1,080 per year if a benazepris/amlodipine combination is used rather than the constituent calcium channel blocker and ACE inhibitor.[13] A study of tuberculosis drugs, used by a very cost sensitive population in Africa, showed that combination fixed dose compounds had far greater annual decreases in prices than the individual components, and in 2002, cost half as much as buying the equivalent single doses.[14]

Market discrimination by firms

When combination products are sold for different indications than are the constituent products, the firm has the ability to engage in price discrimination and increase its overall profits. For instance, customers are usually sensitive to the prices of drugs for chronic

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[11] "All-in one pills for heart disease", Harvard Health Letter July 2004:3
[12] "Combination Drugs", Review of Optometry, August 2004;2-4
[13] Kountz, D.S. "Cost Containment for Treating Hypertension in African Americans: Impact of a Combined ACE-inhibitor/Calcium Channel Blocker". Journal of the National Medical Asscociation 1997;89(7): 457-460
[14] Robert Bwire, "Product costs of fixed-dose combination tablets in comparison with separate dispensing and or co-blistering of anti-tuberculosis drugs", World Health Organization International Publications, 2002. whqlibdoc.who.int/publications/2003/a86263_welcome.pdf

indications and less so to the prices of drugs for acute indications[15]. Thus, a combination drug used for a chronic indication could be priced lower than a constituent component used for an acute indication.

Clinical drawbacks of combination drugs

Fixed ratios

Perhaps the biggest negative feature of unified combination therapy is that these products limit the ability of prescribing physicians to control dosage of the components. If a particular combination is not offered, a patient may be prescribed a non optimal combination. By targeting the"average" or "median" patient, the fixed dosages may not be applicable to a large part of the patient population.[16]

Adverse effects additive

In certain classes such as drugs for diseases of the central nervous system, the side effects are additive, which means a combination produces more side effects than a single component drug at a higher dose. This is presumably because drugs used for central nervous system indications, such as anticonvulsants, have to be dosed above the threshold that causes side effects in order to be effective. Thus, a combination of drugs leads to a combination of side effects, since each of the drugs may cause different side effects.

Prevailing negative attitude

Post World War II, many drug companies marketed effective drugs along with dubious drugs in a unified tablet. This caused the American Medical Association to oppose fixed dose combinations because it limited the physician's ability to decide on which components and dosage to prescribe.[17]

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[15] Kolassa E. M ,*Elements of Pharmaceutical Pricing*,., The Pharmaceutical Products Press, 1997
[16] "Two pills in one", Harvard Heart Letter, June 2004
[17] Herxheimer, "The danger of fixed drug combinations" ,International Journal of Clinical Pharmacology and Biopharmacology 1975 12(1-2): 70-73

This historically negative attitude has hindered the acceptance of combination products. This is reflected in the guidelines that prescribe a less efficacious single antihypertensive as the first line treatment for hypertension, and in the general reluctance to prescribe unified pills.[18]

Economic drawbacks of combination drugs

Exclusionary bundling and patent extension

Exclusionary bundling[19]occurs when a pharmaceutical company has a patented product that is often used in combination with a product that is not patented. The company may price the unified product substantially lower than the sum of the prices of the two component products, at which price it becomes unprofitable for competitors to offer the non patented product alone. Additionally, the company may choose to provide only the unified product, forcing the unprotected component to be bought from the company, thereby further reducing competition for the unprotected component.

For example, if Pfizer produced the sole HDL-raising drug, torcetrapib, and bundled it with its LDL-lowering drug - atorvastatin (Lipitor) – a class of products (statins) which have recently lost patent protection[20] – at a price at which it became unprofitable for other manufacturers of statins to offer their products individually, it would result in exclusionary bundling. This would be especially true if the standard of care for patients with hyperlipidemia becomes a combination of HDL-raising and LDL-lowering medication and if Pfizer did not offer the HDL-lowering drug alone as is its current intention.[21]

Combination therapies: Devices

Drug eluting stents are expected to capture 70% to 90% of the total market for stents.[22] This is just one example of the increasing interest in drug-device combinations. The

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[18] "Guidelines for the Diagnosis and Management of Asthma", Expert Panel Report 2. National Institute of Health, National Heart, Lung and Blood Institute 1997.
[19] Barry Nalebuff ,"Exclusionary bundling" , Yale School of Management, www.law.yale.edu/leo/papers/nalebuff1.pdf
[20] Val Brickates Kennedy ,"Pfizer: Lipitor sales won't fall off a cliff", www.MarketWatch.com, May 2, 2006
[21] "Torcetrapib and Atorvastatin",New England Journal of Medicine, October 6 2005
[22] Robert Roth, "Winning combination", Red Herring, Feb 2003;53-55

table below shows drug-device products currently in development. Pharmaceutical companies that previously exited the device business are increasingly entering joint development agreements with medical device companies to create these combinations. One example is the recent joint development agreement between Medtronic and Genzyme.[23]

In the mix

Some of the new devices making their way through the U.S. Food and Drug Administration.

- **Medtronic Sofamor Danek's InFuse Bone Graft/LT-CAGE fusion device: a metallic spinal-fusion device that combines an inert metal cage for stabilization plus a biologically active bone graft substitute**
- **Ortec's OrCel bilayered cellular matrix: a wound-healing device that incorporates living skin-regenerating cells into an inert matrix**
- **DePuy Orthopaedics' Prostalac: a temporary hip prosthetic device consisting of bone cement and antibiotics**
- **VitaGen's ELAD artificial liver: a liver-assist device that incorporates human liver cells into hollow fiber membranes for kidney dialysis**
- **Novoste's Beta-Cath System: a cardiac catheter tube containing radioactive seeds that provides short-term radiation treatment of coronary arteries to prevent scar tissue from reblocking blood passageways**

SOURCE: Weinberg Group

Table 1: Combination devices, Red Herring Feb 2003[24]

Clinical benefits of combination devices

Invasion – local treatment

One of the major benefits of using drug-device combinations is that it allows the mechanical properties of a device to be augmented by the biologic properties of pharmaceuticals. Drug-device combinations make the underlying mechanical procedure far more successful, particularly in orthopedic and cardiovascular applications, where both mechanical and biological factors are critical for success.

This can be seen in the case of drug-eluting stents, which prevent smooth muscle proliferation on the stents, generally by coating the stents with anticancer drugs. This

[23] "Devices and their desires, Engineers and Chemists get together", The Economist, April 15 2006: 65

[24] Robert Roth, "Winning combination", Red Herring, Feb 2003;53-55

inhibition of cell growth by the drug makes angioplasty far more efficacious, reducing the need for restenting and open heart surgery.[25] Conversely, brain electrodes would have to elute growth factors to prevent the brain from 'growing away' from the implants, which is the normal response of the human brain to medical implants.[26]

In contrast to an oral or injected drug that acts on the whole body, the drug-device combination ensures that the drug is localized to where the action is needed, by the implanted device. For example in drug eluting stents, Taxol, at the site of the stent, prevents proliferation at the location of the implant. There is currently no systemic therapy to prevent this proliferation, presumably because the concentrations required locally at the site of the stent cannot be achieved within the therapeutic range of any drug given systemically.[27]

Clinical drawbacks of combination devices

Complex interactions and regulations

The complex interactions between drugs and devices make clinical testing and approval far more challenging than that of individual products. The drugs need to be tested for efficacy with the device as well as for systemic toxicity. In addition, when biologic components such as cells are used in the device, the manufacturing and quality control can become very complex.[28]

Combination therapies: Diagnostic and therapy

The restriction on the use of Herceptin for breast cancer patients with a high number of estrogen receptors ushered in the era of personalized medicine.[29] This, in turn, has given rise to 'in-house' testing, a way for pharmaceutical firms to bundle a diagnostic or genetic test with the treatment.

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[25] Pedro A. Lemos, Patrick W. Serruys, J. Eduardo Sousa, "Drug-Eluting Stents Cost Versus Clinical Benefit", Circulation. 2003;107:3003

[26] Turner JN, Shain W, Szarowski DH, Andersen M, Martins S, Isaacson M, Craighead H.,"Cerebral astrocyte response to micromachined silicon implants",Experimental Neurology, 1999 Mar;156(1):33-49.

[27] Yang Z, Birkenhauer P, Julmy F, Chickering D, Ranieri JP, Merkle HP, Luscher TF, Gander B,"Sustained release of heparin from polymeric particles for inhibition of human vascular smooth muscle cell proliferation", Journal of controlled release, 1999 Aug 5;60(2-3):269-77.

[28] Robert Roth, "Winning Combinations", Red Herring, Feb 2003

[29] "Personalized medicine: revolutionizing drug discovery and patient care", Trends in Biotechnology, December 2001,19

This vertical integration of testing with treatment exemplifies efforts by the pharmaceutical industry to avoid potential double marginalization (described in further detail below) whereby the diagnostic supplier as well as the pharmaceutical company attempts to extract a margin, raising the price to system wide profit reducing levels.

Merck discovered that in order to make Fosamax, a drug for osteoporosis, successful, it had to lower the price of the diagnostics (bone scans) or suffer from double marginalization. In this case, Merck achieved the integration contractually by promoting products from Lunar Corp., Hologic, Inc., and Compumed.[30]

[30] Association of Strategic Alliance Professionals, June 2003;1 (1), www.strategic-alliances.org

CHAPTER 2: FACTORS AFFECTING UNIFIED COMBINATION DRUG PRICING

Having discussed the various types of combination products and their advantages and disadvantages I will now outline the primary factors that influence the pricing of unified combination pharmaceutical products.

Two of these factors – market factors and component factors -- will be applicable to all combination products and the third - market exclusivity - will be applicable to those combination products that have a component which has some degree of exclusivity, generally in the form of patent protection.

The pharmaceutical pricing chain

After the legislation of a most favored nation clause for the United States federal government, whereby the government must receive the lowest price that a pharmaceutical company has offered any purchaser, there has been a drastic reduction in discounting by pharmaceutical companies, leading even to an increase in prices for some generics. The political factors driving the public sector have perversely reduced discounting in the private sector and have added to the increase in prices as had been previously predicted by critics.[31] In addition, a large fraction of the population does not have prescription drug insurance coverage and must purchase their products at the pharmacy at list prices. Due to these reasons, I will solely use retail prices paid by the private sector for all analyses done in this thesis.

[31] Fiona Scott Morton,"The Strategic Response by Pharmaceutical Firms to the Medicaid Most-Favored-Customer Rules," The RAND Journal of Economics, 1997;28(2)

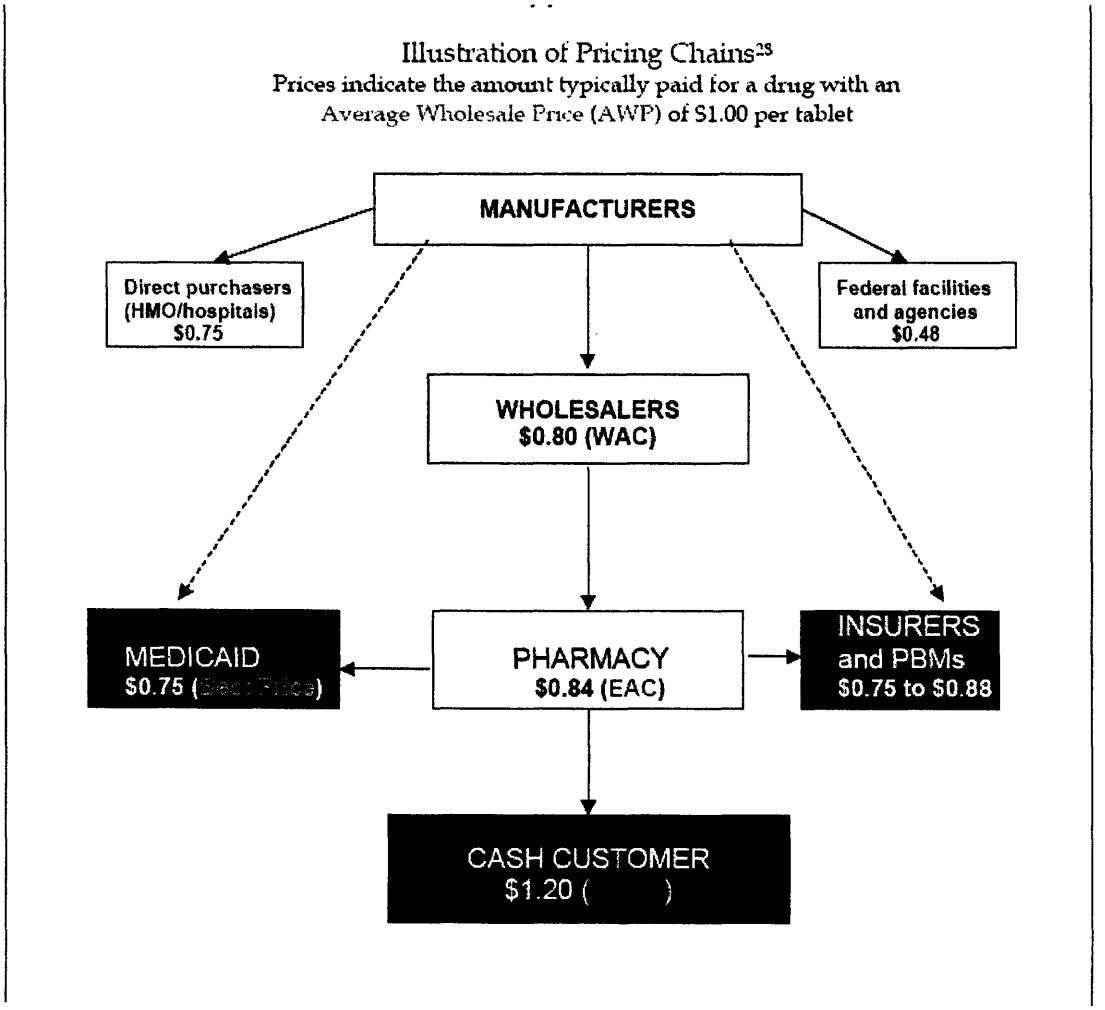

Figure 3: Pricing Chains from "The Profit in Pills: A Primer on Prescription Drug Prices", American Association for Retired Persons[32]

Market factors in the Pharmaceutical Industry

The Elements of Pharmaceutical Pricing, by Mitch Kolassa[33] lists nine primary market factors that a pharmaceutical firm considers when deciding on the price of its product. These are summarized below:

[32] "The Profit in Pills :A Primer on Prescription Drug Prices", American Association for Retired Persons, www.retiredamericans.org/news_theprofitinpills.htm
[33] Kolassa E. M, *Elements of Pharmaceutical Pricing*,., The Pharmaceutical Products Press, 1997

1. *Competitor prices, product features and actions*: A pharmaceutical company has to take into account the pricing by competitors as well as their actions when deciding on its product price. In general, other things equal, later entrants into a market price their products lower than incumbents, presumably to achieve market penetration. In addition, different markets display varying sensitivities to price. Based on this, a company can pursue skimming – pricing its products high to attract high paying customers, parity, or penetration - pricing low - as pricing strategies.[34]
2. *Patient characteristics* i.e., the economic ability of patient to bear the cost of the treatment. Different diseases affect distinct subpopulations with varying abilities to pay. A product for a low income subgroup will generally have to be priced lower than one for a high income subgroup.
3. *Economic value* i.e., the cost-effectiveness and social value of the medication. For example, if a product reduces hospital stays, it can be priced relatively high.
4. *Prescriber decision making*: Prescribers in the market for the product may characteristically be risk averse or be more willing to experiment.
5. *Disease characteristics*: Patients are more willing to tolerate high prices for acute indications than for chronic indications, where they will have to bear the price for a longer period of time.
6. *Company dynamics*: The financial condition of the company and the pressure for immediate profits will have an impact on pricing.
7. *Company financial position*. The ability of the company to sustain a long campaign against incumbents with little or no profit will determine the price at which it can enter the market. A company in a strong financial position can, for instance, weather a price war.
8. *Insurance reimbursement scenario*: When insurance companies are reluctant to add an additional drug to the formulary for the indication, firms may be required to price the product low to gain acceptance.
9. *Public policy and reaction*: Pharmaceutical companies have to weigh the risk of the government or NGOs getting involved in the pricing of highly visible drugs, such as the pricing of drugs for AIDS. In addition if a combination drug is priced

[34] Z. John Lu,William S. Comanor, "Strategic Pricing of New Pharmaceuticals", The Review of Economics and Statistics, February 1, 1998, 80(1):108-118

substantially lower than the components there may be a public outcry about "unfair" high prices for the component drug despite the more complex combination being sold cheaply.

Demand Characteristics for Pharmaceutical Products

The demand curves for drugs are relatively steep (not very price sensitive) and drop off dramatically at market saturation. This is because there are a certain number of patients with the disease who are mildly sensitive to price and once all the patients have access to the drug, there is no further demand. This allows firms to keep relatively high prices, since a drop in price will not increase volume enough to offset the losses from the lower price.[35]

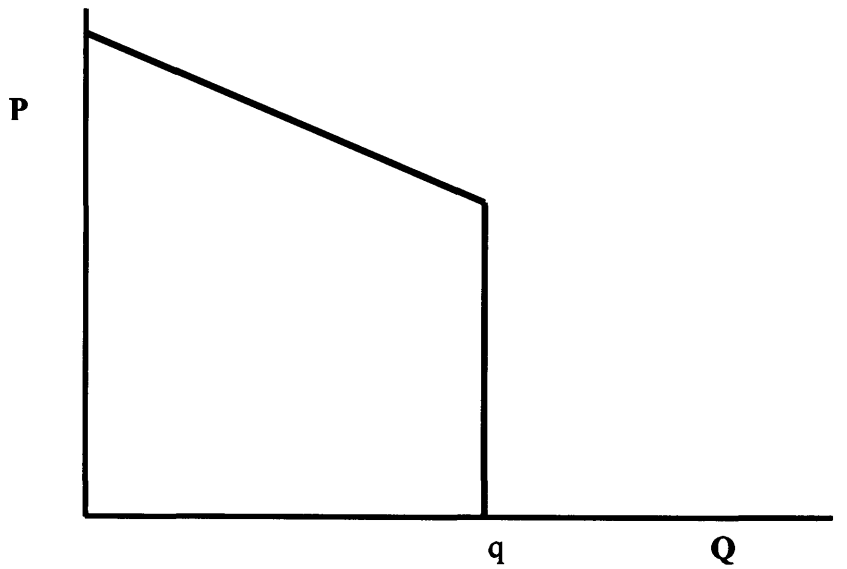

Figure 4: Demand Characteristics for pharmaceutical products.
P = Price Q= Quantity q= number of patients with disease

[35] Jayashree Watal, "Pharmaceutical Patents, Prices and Welfare Losses: Policy Options for India Under the WTO TRIPS Agreement", The World Economy, May 2000;23 : 733

Component factors

Component factors, for the purpose of this thesis, refer to the individual market prices of the components of a combination product. Although variable costs such as costs of manufacturing and materials are not a large proportion of the retail price of a drug, the prices of combination products can be expected to exhibit a relationship to the market prices of its components. The form of this relationship is affected by a number of other factors such as the firm's fear of cannibalization of the market for the components.

Market exclusivity factors

In the presence of market exclusivity, such as when one or more of the components of a combination drug is patented, additional factors, termed market exclusivity factors in this thesis, come into play.

Double Marginalization

Double marginalization occurs when the products of two non-integrated monopolies are required to deliver a single combination product to the consumer. Each firm, being a monopoly with market power, will price its product at a markup over its marginal cost, resulting in the creation of two margins or what is therefore called "double marginalization".[36]

Consider two unrelated firms – Company A that has a monopoly on component A of a combination drug, and another unrelated monopoly Company B that buys component A from Company A, and adds another component that it produces to produce a final product B. Company B then sells this combined product B to the consumer. For this analysis, initially let us assume that the components have no separate value, i.e., they have to be consumed together to obtain the required therapeutic effect. Let us also assume that the demand curve for the final combination product is linear and that the marginal costs of producing the products are negligible, i.e., the primary costs are R&D and fixed plant costs and the variable costs are close to zero.

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[36] Robert Pindyck, Daniel Rubinfeld, *Microeconomics*, Fifth edition ,Prentice Hall,2001:369,392-403, 402-403

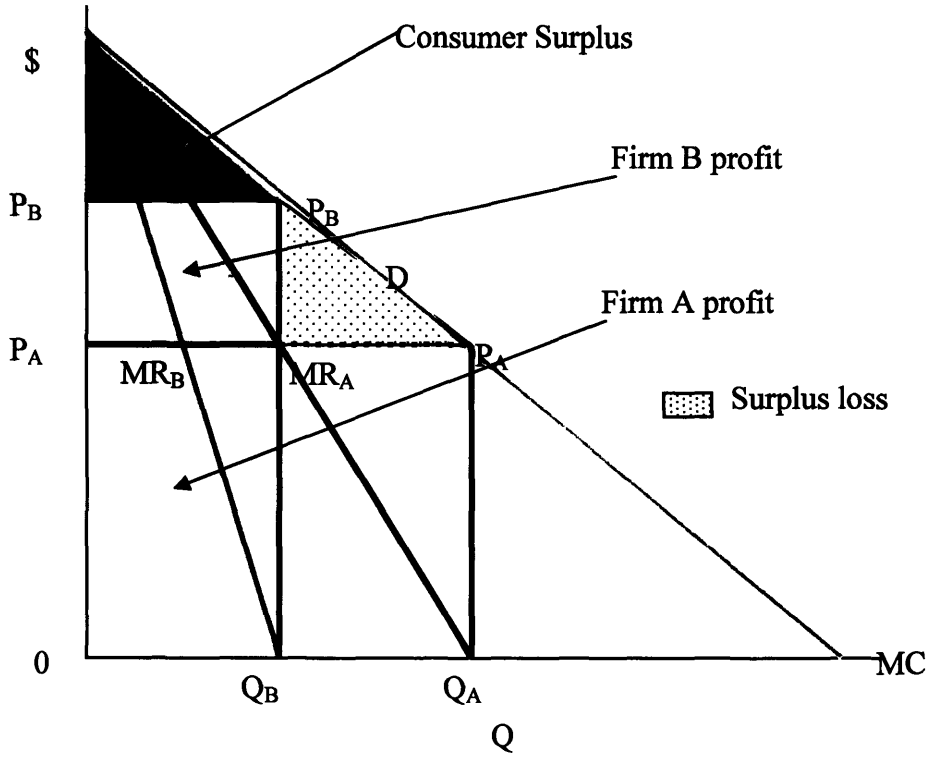

Figure 5: Double marginalization: MR_A marginal revenue for Firm A, MR_B marginal revenue for Firm B, MC marginal cost (0), Q quantity, P price.

Let us first consider Firm A. Since Firm A is a monopoly, to maximize its profit it will sell a quantity of products Q_A, at which its marginal revenue MR_A is equal to its marginal cost (0). It will price its product at a price of P_A

Firm B, will in turn, take this price P_A as its input price and produce the quantity of the combined product that maximizes its profit. To do this it will set its marginal revenue equal to its marginal cost. Since its net marginal revenue is the difference between what it pays Firm A and what it can price the combined product in the market, its net marginal revenue curve MR_B will be twice as steep as MR_A - the marginal revenue curve of Firm A. This will result in a quantity Q_B being produced and sold to the market at price P_B. From the graph we can see that Q_B is less than Q_A and that P_B is higher than P_A. Mathematically I will now show that Q_B will be one half Q_A and one fourth the quantity produced in a perfectly competitive market, a market in which no producer has pricing power.

Let us represent the market demand curve by

$$P = a - bQ$$

where P=price, Q=quantity, a= vertical axis intercept and b=slope of the demand curve.

Perfectly Competitive Market

In the case of a perfectly competitive market, where there are no monopolies present, marginal revenue will equal marginal cost, which in this case is zero i.e. P=0. Hence

$$0 = a - bQ, \text{ and}$$

$$Q = a/b \qquad (2.1)$$

Single Monopoly

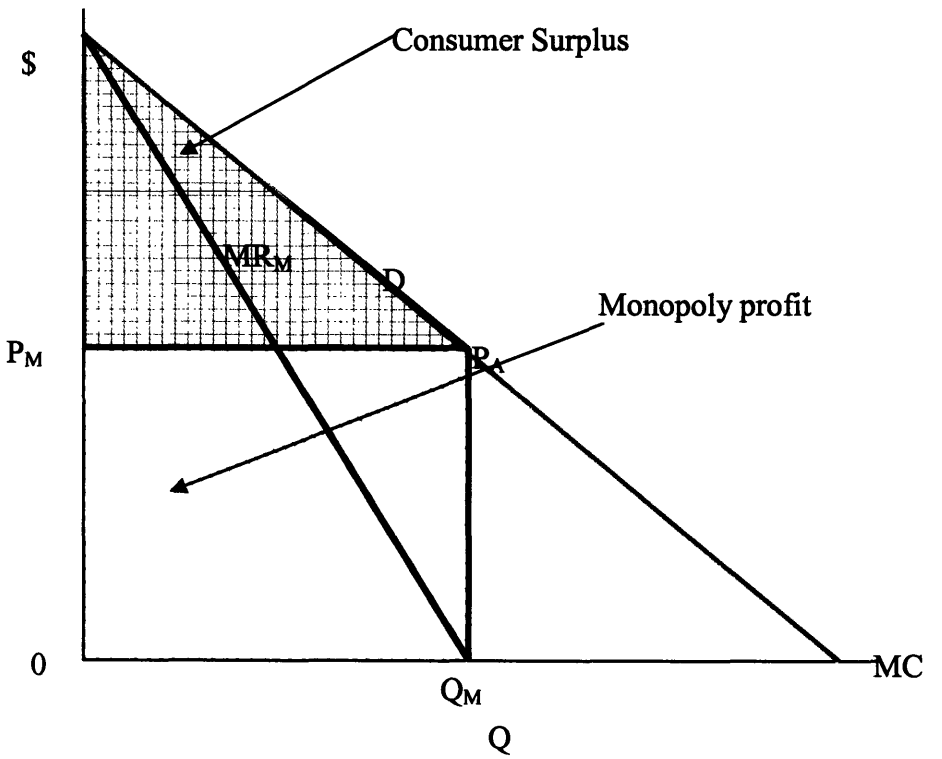

Figure 6: A single monopoly will produce quantity Q_M at a price of P_M

In the case of a single monopoly the firm sees the aggregate market demand as its demand. The revenue (R) of the monopoly is *Price* * *Quantity*

$$R = PQ = aQ - bQ^2$$

The marginal revenue can be obtained by taking the derivative of revenue with respect to quantity

$dR/dQ = a - 2bQ$

The monopoly will produce a quantity of products where its marginal revenue is equal to its marginal costs – in this case zero.

$a\text{-}2bQ = 0$, implying that

$Q_M = ½\ a/b$

(2.2)

Two Monopolies

Now consider two monopolies, Firm A and Firm B. The revenue R of Firm A is *Price * Quantity*:

$R=PQ = aQ - bQ^2$

The marginal revenue, i.e. incremental revenue for each additional product produced can be obtained by taking the derivative of revenue with respect to quantity.

$dR/dQ = a - 2bQ.$

For Firm B, its net marginal revenue will be the revenue it receives from each additional product it sells taking into account the per unit price of its input from Firm A. It will therefore perceive the marginal revenue curve of Firm A as its demand curve i.e. its demand curve is

$P = a - 2bQ$

Its revenue R will be $P*Q$:

$R=PQ = aQ - 2bQ^2.$

The net marginal revenue from each additional product it sells will be the derivative of its revenue with respect to its quantity

$dR/dQ = a - 4bQ.$

To maximize profits, Firm B will produce a quantity of products where the net marginal revenue will be equal to marginal cost.

$a\text{-}4bQ = 0$

which implies that, for Firm B,

$Q= ¼\ a/b$ (2.3)

Thus, when there are two separate monopolies that are required to bring a product to market, the quantity produced will be less than that produced by a single monopoly in control of both components. The total surplus, i.e. the profit of the two firms minus P_B-Q_B

plus consumer surplus - is less than the total surplus of a single monopoly – the profit $P_A{}^*Q_A$ plus consumer surplus. This total loss is marked in Figure 5. Hence, double marginalization results in less total surplus than would occur were the two unrelated monopolists combined into a single integrated firm.

I will now show that when the marginal cost of the two products is not zero and the marginal cost of firm A is MC_A and the marginal cost of firm B is MC_B , these qualitative results continue to be valid. The marginal revenue of the two firms remains the same, since the demand curve is unchanged, i.e. firm B's marginal revenue curve is twice as steep as firm A. The quantity produced by a single monopoly will be

$$\text{Marginal revenue} = a - 2bQ = \text{marginal cost} = MC_A + MC_B$$

$$Q = \tfrac{1}{2}\,(a - MC_A - MC_B) / b \qquad (2.4)$$

In the case of two monopolies, the double marginalization scenario

$$\text{Marginal revenue} = a - 4bQ = \text{marginal cost} = MC_A + MC_B$$

$$Q = \tfrac{1}{4}\,(a - MC_A - MC_B)/b \qquad (2.5)$$

This socially undesirable outcome was first described by Augustin Cournot in 1838, in an analysis of the market for brass that required two complementary inputs, zinc and copper, controlled by independent monopolies. In Cournot's analysis, each monopolist supplier sets his unit price according to a reaction curve that takes into account the price set by the other input supplier resulting in double marginalization.[37] This outcome will also occur for combination therapies in which the two components are controlled by unrelated monopolies. The elimination of double marginalization, by merger or contracts is therefore socially desirable and has been supported by merger authorities.

Bundling

Bundling[38] is the practice of selling two or more products as a single package. This is done either as pure bundling, where the two individual products are available only in a

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[37] Serdar Dalkir, David Eisenstadt, Ari Gerstle and Robert T. Masson, "Complementary Goods, Monopoly vs. Monopoly Power: A Reassessment of Merger Effects", Cornell University 2002, Unpublished

[38] Robert Pindyck, Daniel Rubinfeld, *Microeconomics*, Fifth edition ,Prentice Hall,2001:369,392-403, 402-403

bundle and are not sold separately as individual products, or as mixed bundling, where the products are available both as individual products as well as in bundled form.

Bundling is a viable option when the values of the component products to customers are negatively correlated. This allows a firm to offer a bundle of the two products that increases total consumption by the consumer and increases the value to the firm by selling more of the products, for a greater total profit, than would have been sold at individual market prices. Bundling also occurs when firms charge more for products with large positive networks.

Bundling of consumer drugs is common, as in the case of multivitamins and cough syrups, where bundling reduces the number of products that have to be bought by a consumer for a particular use. In addition to this co-packaging for convenience, several components are included in the formulation that the customer may have not have otherwise purchased individually due to their low added utility- which is a case of economic bundling.[39]

In this study of unified combination drugs, I will analyze prices of products when firms engage in mixed bundling, wherein the component products are available separately as individual drugs and also together as a bundle.

Tying

Tying[40] is the requirement imposed by companies that certain products must be purchased in combination.

Tying is a frequent occurrence in the health care industry, where companies often sell a product that requires a disposable component for each use. For example, an imaging device that only works with disposable film from the same manufacturer will exhibit tying. Tying allows medical device companies to charge a premium over marginal cost for the disposables, causing heavy users to pay more while charging a low price for the core

[39] David Evans, Michael Salinger,"An empirical analysis of bundling and tying: Over-the-counter pain relief and cold medicines",CESIFO working paper no. 1297, Industrial Organization, presented at CESIFO, July 2004

[40] Robert Pindyck, Daniel Rubinfeld, *Microeconomics*, Fifth edition ,Prentice Hall,2001:369,392-403, 402-403

device, making it affordable for light users. In economic terms, this becomes a two-part tariff. Unlike mixed bundling, where the products are available individually as well as in a bundle, tying generally forces all products to be purchased from one seller.

CHAPTER 3: HYPOTHESES CONCERNING THE PRICING OF UNIFIED COMBINATION DRUGS

I will now offer hypotheses concerning the relationships between the various factors that influence the pricing of unified combination products. This relationship will be further analyzed for two classes of unified combination drugs – those with market exclusivity and those without.

The three factors I have discussed earlier – component factors, market factors and exclusivity factors - will have varying influences on the price of combination drugs. The following hypotheses will attempt to predict the influence of these factors on the price of the unified combination product. Hypothesis 1 has a weak (1a) and a stronger (1b) version. Hypothesis 2 will introduce issues concerning market exclusivity.

HYPOTHESES

Hypothesis 1

1a

Prices of unified combination drugs will be positively correlated to the sum of the prices of the components, despite the low marginal costs of manufacturing pharmaceuticals. Specifically, despite the weak relationship between manufacturing cost and retail price, firms will have to take into account cannibalization of sales of the individual products, as well as societal scrutiny and price their combination products in relation to the prices of the components.

1b

The price of unified combination products will be less than the sum of the prices of the components. Although analysis of reasons for this are beyond the scope of this thesis, I conjecture that combined products will on average be priced lower due to factors such as savings on fixed costs and reimbursement limits. The added regulatory burden of obtaining separate FDA approval for the combined product is a fixed cost and will not have a strong influence on the retail price of the combination product.

Hypothesis 2

The relationship between the sum of the price of the components and the price of the combined product will be significantly modified by market exclusivity. Specifically, the presence of exclusivity for any of the components will *decrease* the price of the combined product relative to the sum of the prices of its components.

For combination products with exclusive components, i.e., protected by patents, the market exclusivity factors described above – elimination of double marginalization, tying or bundling, including exclusionary bundling, may occur. All of these factors tend to lower the price of the combined product in relation to a non-exclusive combination with the same constituent costs. The price of these combination products with an exclusive component will also have a stronger correlation with the sum of component prices than combination products without any exclusive component, i.e., component factors dominate over other factors for exclusive products.

Prices of combination products with non-exclusive products, where there are no market exclusivity factors at play, will thus have a relatively higher price when compared to products with an exclusive component. These products will have a lower correlation with the sum of component prices than products with an exclusive component since these firms do not have to take into account cannibalization of a protected component drug and will therefore be more responsive to other market forces.

CHAPTER 4: METHODS

Sample and data sources

The list of all unified combination drugs sold in retail was obtained by running a query in IMS Dataview[41], selecting all products with more than one component. This list was refined, first by only including tablets and capsules and removing other delivery formulations such as intramuscular or intravenous. Next, drugs that did not have separately sold individual components were removed from the list. Two web based sources – www.Epocrates.com and www.Medicare.gov -- were used to determine whether the components were available. The refined list consists of 35 unified combination drugs for which data about the combined price, individual component price and market exclusivity status are available.

Each unified combination drug was input into the Medicare website to obtain the most common dosage used and the exclusivity status of the drug and the components. The formulation of the unified combination drug and the prices of the individual components were then obtained from the Epocrates website. In a few cases, the exact dosage was not available for a component and the price from the closest dosage was used. The individual steps followed to obtain the data are detailed in the Data Appendix. This data was compiled on Feb 15, 2006 and reflects the retail prices and market status as of that day; all prices are for monthly (30 day) prescriptions.

Variables

The dependent variable is the monthly price of the combined unified drug.

Explanatory variables

To understand the relationship between the sum of the prices of the components and market exclusivity to the retail price of the combined drug, I used three explanatory

[41]IMS Dataview contains pricing data from a variety of sources including most pharmacies in the United States, www.imshealth.com.

variables – a dummy variable representing exclusivity, exclusivity times the sum of the prices and the sum of the prices squared. Exclusivity was used as an explanatory variable to assess whether the combination price is statistically affected by the presence of exclusive components. Exclusivity times the sum of the prices was used to quantify the relationship between the sum of the prices of the components and the combined product price, for products with exclusivity. As a third explanatory variable and to avoid complications such as perfect colinearity, I used the square of the sum of component prices rather than the sum of component prices.

In mathematical terms, letting *Pc* be the price of the combined drug, *P1 and P2* be the prices of the component drugs, *EX* be a dummy variable equal to 1 if one of the component drugs have exclusivity, else zero, and letting *b0, b1, b2* and *b3* be parameters to be estimated empirically, the equation I specify is as follows:

$$Pc = b_0 + b_1*EX + b_2*EX*(P_1 + P_2) + b_3*(P_1 + P_2)^2 + e, \quad (4.1)$$

where e is a random error term, assumed to be independently and identically normally distributed with mean zero and constant variance.

Note that with this specification, the following relationships are implied:

$$\Delta Pc/\Delta(P_1 + P_2) = b_2EX + 2b_3*(P_1 + P_2) \text{ and} \quad (4.2)$$

$$\Delta Pc/\Delta EX = b_1 + b_2*(P_1 + P_2), \quad (4.3)$$

where the delta symbol Δ refers to "change in" or "difference operator" (partial derivatives cannot be used here since *EX* is a discrete rather than continuous variable).

Hypothesis testing

Hypothesis 1a predicts that $\Delta Pc/\Delta(P_1 + P_2)$ will be positive. This implies that

$$b_2EX + 2b_3*(P1 + P_2) > 0$$

For this relationship to hold for non-exclusive drugs (*EX* =0), the term $2b_3*(P_1 + P_2)$ must be positive implying that

$$b_3 > 0 \quad (4.4)$$

Hypothesis 1b predicts that the increase in price for every unit increase in the price of the components is less than one, i.e., the combined product price rises more slowly than

the constituent product prices ($\Delta Pc/\Delta(P_1 + P_2) < 1$). Testing this hypothesis for non-exclusive products ($EX=0$) implies that for this hypothesis to hold, it is necessary that

$$2b_3*(P_1 + P_2) < 1.$$

This (assuming a positive b_3) cannot be true for infinitely large values of $P_1 + P_2$ but for the range of values in this dataset ($max(P_1 + P_2) = 235$) it implies that

$$2b_3*(235) < 1$$

$$b_3 < 0.0021 \quad for \quad max\,(P_1 + P_2) = 235 \tag{4.5}$$

Hypothesis 2 predicts that component market exclusivity will reduce the price of the combined product i.e.

$\Delta Pc/\Delta EX < 0$, which from Eqn. (4.3) requires that

$b_1 + b_2*(P_1 + P_2) < 0$, which implies

$$b_2 < 0 \tag{4.6}$$

Additionally for $\Delta Pc/\Delta EX < 0$ either

$$b1 < 0 \tag{4.7}$$

or if b_1 is positive, hypothesis 2 is true for a range where

$$b_1 > 0 \text{ for } b_2*(P_1 + P_2) > - b_1 \tag{4.8}$$

The hypotheses concerning the pricing of combination products therefore result in the following restrictions on the parameters I estimate:

Hypothesis tested	Applicability	Predictions	Range
Hypothesis 1a	general	$b_3>0$	
Hypothesis 1b	limited	$b_3< 0.0021$	max =255
Hypothesis 2	general	$b_2< 0$	
	general	$b_1 < 0$	
	limited	$b_2*(P_1+P_2) > -b_1$	$b_1 > 0$

Table 2: Hypotheses and predictions

Statistical analysis

The data was compiled in Excel and statistical analyses were performed using the regression function of the Microsoft Excel data analysis package. To test the hypotheses, I will perform the following analyses:

First, I will perform multivariable regression analysis to assess whether the explanatory variables adequately explain variation in the dependent variable. I will test the result for validity via the equation *F*-statistic, the *adjusted* R^2 and an analysis of the residuals. The resulting equation will posit a way to derive the price of the combined product based on exclusivity and the price of the components. In addition to the hypothesis testing described above, to validate hypothesis 2, I will segregate the data based on market exclusivity, and compute the correlation between these two sets of variables (combination price and sum of prices of components) for both groups (with and without exclusivity).

CHAPTER 5: RESULTS

Statistical Results

I performed a multivariable regression analysis with the explanatory variables and dependent variable discussed above. Below is the output from the analysis:

Regression Statistics	
Multiple R	0.918
R Square	0.843
Adjusted R Square	0.827
Standard Error	16.517
Observations	35.000

ANOVA

	df	*SS*	*MS*	*F*	*Significance F*
Regression	3.000	45256.768	15085.589	55.298	1.51E-12
Residual	31.000	8456.953	272.805		
Total	34.000	53713.720			

	Coefficients	*Standard Error*	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	29.962	3.723	8.048	0.000	22.370	37.555
Exclusivity	37.833	18.331	2.064	0.047	0.446	75.220
price sum ^2	0.0056	0.001	4.118	0.000	0.003	0.008
e*Sum	-0.604	0.362	-1.669	0.105	-1.343	0.134

Table 3: Regression output. Dependent: price. Independent: exclusivity, square of the sum of prices of components exclusivity times sum of prices

The equation *F*-test is significant at $p<0.0001$ indicating that variations in the explanatory variables are significantly explaining variability in the dependent variable.

84% of the variation in the price of the combined product is explained by the variation in the explanatory variables *(R^2 = 0.843 and Adjusted R^2 = 0.82)*. The coefficient estimates on *EX* (exclusivity), $(P1+P2)^2$ (square of total constituent price) are each statistically significant at $p<0.05$, although the estimate on the exclusivity-price sum interaction variable is not significant.

The results of the regression are

b_0= 29.962 (8.048)*

b_1= 37.833 (2.064)*

b_2= -0.604 (1.669)

b_3= 0.0056 (4.118)*

(Note: Values in parentheses are the absolute values of the t-statistics. * denotes significance at a 5 percent (two-tailed) level.).

The estimated equation for the least squares regression is therefore:

$$Pc = 29.962 + 37.83 * EX + 0.604 * EX * (P_1 + P_2) + 0.0056 * (P_1 + P_2)^2 \qquad (5.1)$$

where:

Pc is price of the combined drug,

P_1 and P_2 are the price of the component drugs,

EX is a dummy variable equal to 1 if one of the component drugs have exclusivity, else zero.

Below is an analysis of the delta relationships (equation 4.2 and 4.3) at the 10th percentile rank, at the median, and at the 90th percentile rank.

	P_1+P_2	Non Exclusive	Exclusive
Rank 4 (10th percentile)	14.00	0.16	-8.30
Rank 17 (median)	32.98	0.37	-19.56
Rank 32(90thpercentile)	68.05	0.77	-40.36

Table 4:ΔPc/Δ(P1 + P2) relationships (equation 4.2) at various ranks

	P_1+P_2	$\Delta Pc/\Delta EX$
Rank 4 (10th percentile)	14.00	29.37
Rank 17 (median)	32.98	17.90
Rank 32 (90thpercentile)	68.05	-3.30

Table 5: ΔPc/ΔEX relationships (equation 4.3) at various ranks

From Table 4 we can see that at the 10th percentile of the dataset (sorted by total component price), for every $1 increase in the component price, non-exclusive products

increase slightly by 0.16 and exclusive products decrease in price by $8.30. As the component prices become higher the exclusive product discounting increases. Presumably at higher prices for exclusive products the market exclusivity factors, which would cause prices to decline, are in effect and are less so at lower prices. The non-exclusive product price delta remains small. These results also show that the change in component price has a much greater effect for exclusive products than for non-exclusive products.

Table 5 also shows that as the total component price increases, the premium for exclusive products over non-exclusive products becomes a discount. At total component prices greater than 63.05, exclusive products have a discount and below that a premium to the price of non-exclusive products having the same total component costs.

Goodness of Fit

A White test yields an insignificant *F*-statistic *(*1.06, significance 0.37*)*, allowing us to not reject the assumption of homoskedasticity.

Below is the table of predictions along with the results obtained from the regression.

Hypothesis tested	Applicability	Predictions	Range	Result	True/False
Hypothesis 1a	general	$b_3>0$		b3>0	True
Hypothesis 1b	limited	$b_3< 0.0021$	max =255	b3 > 0.0021	False
Hypothesis 2	general	$b_2< 0$		b2<0	True
	general	$b_1 < 0$		b1>0	False
	limited	$b_2*(P_1+P_2) > - b_1$	$b_1 > 0$		True for $P_1+P_2 > 63.05$

Table 6: Hypothesis predictions with computed values

Since hypothesis 1b does not hold but hypothesis 2 does *($b_2 < 0$)* hypothesis 1b is applicable to exclusive drugs for a range

$$2b_3*(P_1 + P_2) < 1 - b_2$$

i.e., where

$$51.61 < P_1+P_2 < 233.05$$

Below is a plot of the relationship of combined product price to the sum of component prices for exclusive and non-exclusive drugs based on the equation derived from the least squares regression.

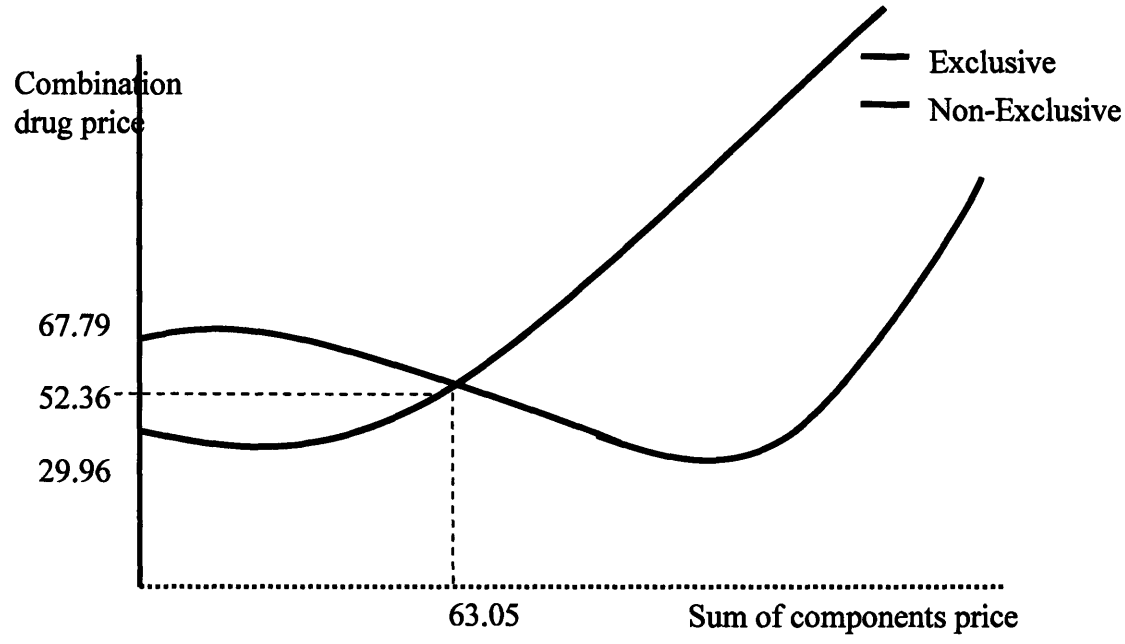

Figure 7: Plot of exclusive and non-exclusive combination drug price vs. sum of component price

Looking at the plots of combined product price against the sum of components price, we see that exclusive products reveal far more correlation than non-exclusive products. The correlation coefficient (or *multiple R* for a regression of price against total constituent price) for exclusive products is 0.90 (with a significant *F-statistic* $p<0.001$), which is much larger than the 0.19 for non-exclusive products (*F-statistic* not significant).

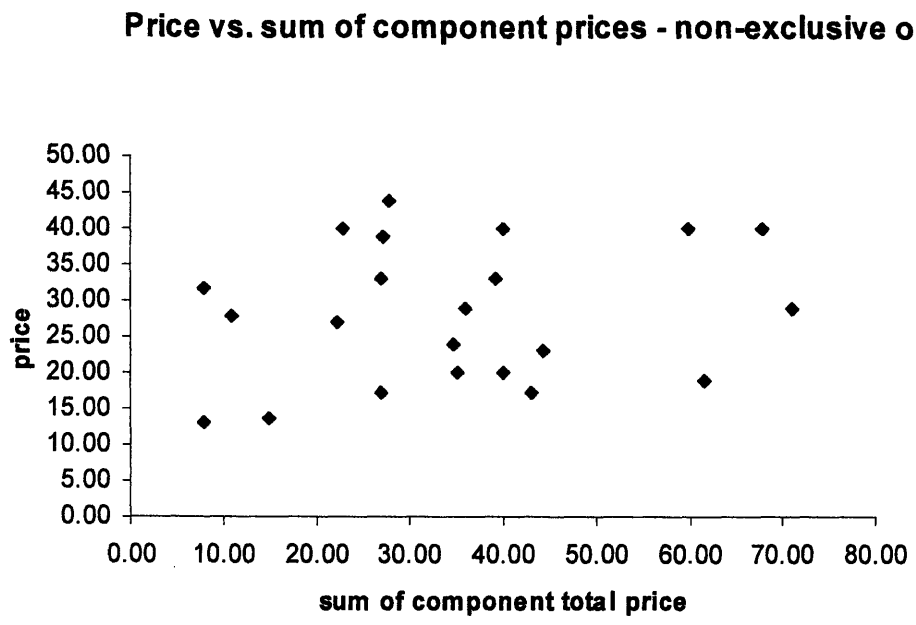

Figure 8: Plot of price (Y) vs. sum of components total price. Non-exclusive only.

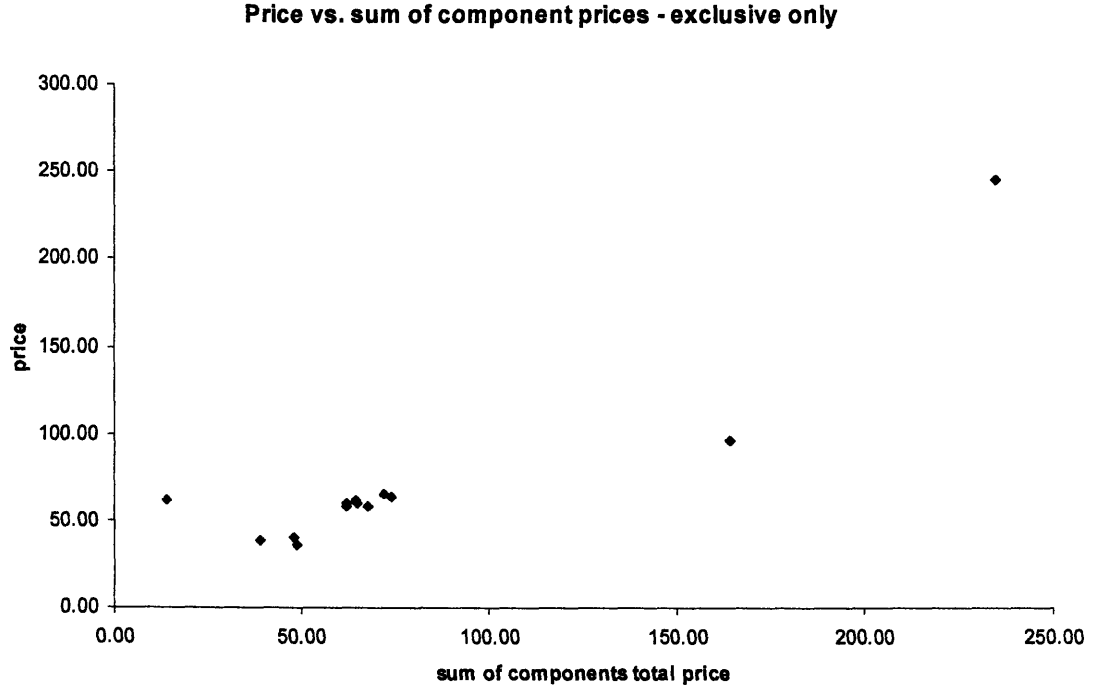

Figure 9: Scatter plot of price (Y) vs. sum of components total price. Exclusive only.

Discussion

Hypothesis 1a predicted that over all types of products (exclusive and non-exclusive) unified combination prices will be lower than the sum of the prices of the constituents. In fact, the mean price for the unified combination product was $48.90 and the mean of the sum of the prices of the component drugs was $46.77, indicating a slight combination premium. In addition, this difference is not statistically significant and we will have to *reject hypothesis 1b* since there is no empirical support for it. We *cannot, however, reject weaker hypothesis 1a* that the unified combination product price is positively correlated with the sum of component prices. Moreover, as discussed in the results section above, hypothesis 1b does hold for a range of prices for exclusive products. For exclusive products, whose sum of component prices are between 51.61 and 233.05, the combined product is priced at a discount to the sum of its constituents prices.

One possible reason for the above result could be that the added costs, including added regulatory requirements for the combination product, may offset the marginal cost reductions due to lower packaging and manufacturing costs.

This regression reveals two primary components of the price of the unified drug.

The first is $29.96 + 0.0056 $(P_1 + P_2)^2$ that slowly increases with the increase of the square of the sum of components prices. The second component is a modifier if the drug has an exclusive component of $37.83 – 0.6 * (P_1+P_2).

The results suggest that there is relatively large exclusivity premium (~$37.83) if the prices of the components of the drug are relatively cheap. It may be the case that, in this scenario, the exclusive drug in a stand-alone form is sold in a highly competitive market, which explains the low prices of the components, and the combined drug offers an opportunity for the company to enter a less competitive and more lucrative market.

As the prices of the component drugs become higher, this premium declines and becomes a discount at total component prices greater than $63.05. Hypothesis 2 predicted that drugs with an exclusive component will be less expensive than those without an exclusive component. Based on the results of the least squares regression *we cannot reject hypothesis 2 for combined drugs whose total component costs are*

greater than $63.05. Total component costs are above $63.05 for roughly two-thirds of the sample analyzed. One explanation for the change from a premium to a discount for products with an exclusive component could be that, at high component prices, the combination product may be increasingly influenced by the market exclusivity factors of bundling, exclusionary bundling, or elimination of double marginalization.

If both components were hitherto run by separate profit centers that sold their products at market price, the combined product will eliminate double marginalization. This is because in a well managed firm the transfer price of the exclusive ingredient would be set at its marginal cost and not the monopoly price achieved for that component in its market.[42] This elimination of double marginalization would create downward pressure on the price of the combined product. If the combined product employs economic bundling, its price will be less than the sum of the components prices, again exerting downward pressure on the price of the product. Exclusionary bundling also results in a downward pressure on the combined product price, whereby the drug company is attacking the producer of the other component in the combination, by pricing the combination at a discount.

The prices of combination drugs with an exclusive component show a stronger relationship with their components prices, possessing both a significant *F*-statistic as well as a strong correlation coefficient, than do combination drugs without an exclusive component. This suggests that products with exclusive components are more influenced by component factors and products with non-exclusive components are more influenced by other factors – presumably market factors.

The plausible reasons, described above, for a premium or discount in the pricing of products with an exclusive component in relation to products without an exclusive component are summarized in Figure 14 below. Since non-exclusive products are assumed to be responding primarily to market pressures, the relative premium and discount of exclusive product prices are posited to be due to profit-seeking entry and the influence of market exclusivity factors.

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[42] Robert Pindyck, Daniel Rubinfeld, *Microeconomics*, Fifth edition ,Prentice Hall,2001:369,392-403, 417-420

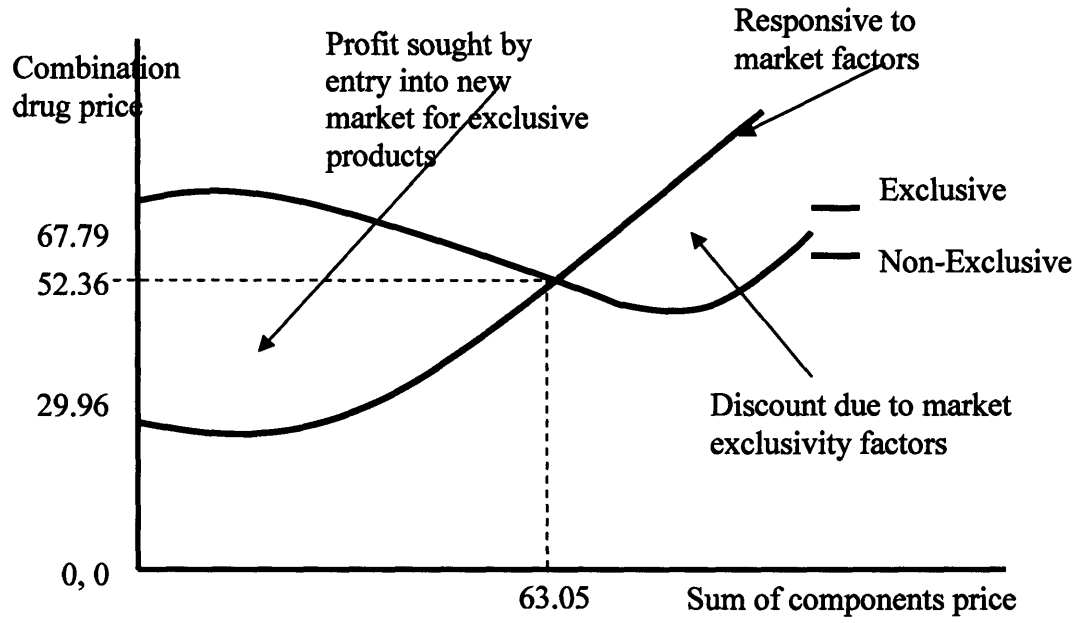

Figure 10: Pricing of exclusive and non-exclusive products relative to prices of components with plausible reasons for the premium and discount of exclusive products

Implications for personalized medicine

At first glance, it may seem plausible that the advent of personalized medicine might adversely affect the economic feasibility of commercializing further unified combination drugs, since the doses would have to be tailored for each individual. This, however, may not be the case.

One of the major reasons for different doses having different efficacy in different individuals has been the idiosyncratic rates of metabolism of drugs by different individuals. This difference in metabolism can be used to broadly categorize the individuals into slow, normal, and fast metabolizers for different drugs.[43]

In most cases, as in that of the gene CYP2D6 that transcribes drug metabolizing enzymes, this happens due to gene duplication. Multiple copies result in discrete increments in the rate of metabolism of drugs. To address this, combination drugs can

[43]Jan van der Weide, Linda S W Steijns, "Cytochrome P450 enzyme system: genetic polymorphisms and impact on clinical pharmacology", Annals of Clinical Biochemistry,1999;36:722-729

be provided in fixed doses, corresponding to the number of copies of genes, thereby limiting the number of combinations that need to be manufactured.

Limitations

This study was conducted on a small sample from only one class of combination products – unified combination drugs. Extrapolating these conclusions for all drug/drug, drug/device, or drug/diagnostic combinations will have its limits.

In addition, as explained in Chapter 1, there are several prices that could be used to conduct this study. Using wholesale prices rather than retail prices could yield different results. Using international prices, which are very different, due to the single buyer structure of most of those markets could also substantially change the results. The factors analyzed in this thesis are in effect at the manufacturer level of the supply chain. The prices used were, however, retail prices. Discrepancies in margins for exclusive and non-exclusive products at the retail level could affect the results of this thesis.

A review of pharmacology shows that even in the case of antibiotics, the theoretical superiority of a combination drug - producing a better result with fewer side effects – has not been adequately demonstrated, except in cases such as tuberculosis and AIDS. Combination drugs may, therefore, have a narrow area of applicability.

This study also has limited analysis of oncology drugs, wherein a combination is the preferred mode of treatment. This is because, despite the widespread use of combination therapies in oncology, there are few unified combinations available.

It is, in fact, in oncology that these hypotheses could be very interesting. Avastin, priced at $200,000 per patient per year, may be cheaper as a component of a combination drug if Genentech were encouraged to produce a combination. The lack of analysis of this important class may limit the use of this study.

Future research

Expanding the study to remove the limitations mentioned above would make the analysis and conclusions more complete. A detailed study of drug/device- and

drug/diagnostic-pricing relationships would be most interesting. In addition, these fields can build on previous studies done on two-sided markets, where a device could serve as a platform for a drug.

Other related studies[44] suggest that the factors studied in this thesis also influence combinations of two protected products. Branded-branded combination products that are cannibalizing an existing market discount on average 5.5%, while branded-generic combinations discount 22%. In new markets entered into by combinations, the former discounts 2% and the latter 5%. This suggests that firms differentiate unified combination product prices both on the market exclusivity position and their pursued strategy, of expansion, defense, or exclusionary bundling. Incorporating data from these studies could provide a more general conclusion.

Conclusions

Unified combination product prices are related to the market prices of their components. The effects of component prices vary at different pricing levels and by exclusionary status; inexpensive exclusive components lead to a more expensive combination product, more expensive exclusive components to a relatively less expensive combined product, while non-exclusive components lead to a slightly more expensive combined product.

It is evident that the market exclusivity status of the drugs strongly influences the relationship between combination product prices and the prices of their constituent elements. For exclusive components, the relationship between component prices and unified combination prices is very strong. For non-exclusive components, that relationship appears to be dominated by other factors, presumably market factors. For roughly two thirds of the products studied, exclusive products are less costly relative to non-exclusive products with the same component costs. These results are consistent with the hypothesis that, for this class of exclusive combination drugs, the elimination of double marginalization by efficient transfer pricing and economic and exclusionary

[44] "Pricing Drivers of Combination Therapies - Product Premiums Scarcely Seen", Healthcare reports by Data Monitor, May 2005

bundling, lowers the price of the unified combination drug relative to the price of its constituents.

The most compelling case made by this thesis is that, payors and policy makers should encourage the creation of combination drugs by pharmaceutical companies that market an expensive patented drug that is currently used in combination therapy with another drug. The resulting combined product will most likely be less costly than the sum of prices of the individual components.

Payors, policy-makers and practitioners should update current guidelines and make unified combination drugs the first line of treatment for indications where combination drugs have a higher efficacy than single drugs, such as, in the treatment of AIDS, hypertension and cancer. This thesis shows that combined drugs are, in general, no more expensive than the constituent drugs and have added clinical benefits such as increased compliance.

ACKNOWLEDGEMENTS

This thesis would not have been possible without the dedication and coaching provided by Dr Ernst Berndt (MIT Sloan). His tireless efforts are truly remarkable.

I would also like to thank Dr Rebecca Betensky (Harvard School of Public Health) and Michael Magnani (BEP '09) for their assistance in the data analysis.

DATA APPENDIX

Sample data

drug	formulation	sum comp	unified price
DIOVAN HCT SMRY 0398 NVR	hydrochlorothiazide/valsartan	64.98	59.99
HYZAAR SMRY 0595 MSD	hydrochlorothiazide/losartan	73.98	62.99
BENICAR HCT SMRY 0703 SKY	hydrochlorothiazide/olmesartan	62.18	58.3
AVALIDE SMRY 0599 BMP	hydrochlorothiazide/irbesartan	61.98	59.99
MICARDIS HCT SMRY 0101 B.I	hydrochlorothiazide/telmisartan	64.63	61.21
ATACAND HCT SMRY 1000 AZN	candesartan/hydrochlorothiazide	71.98	65.11
TEVETEN HCT SMRY 1202 KOS	eprosartan/hydrochlorothiazide	68.05	58.20
BENAZEPRIL/HCTZ SMRY 0000 USA	benazepril/hydrochlorothiazide	32.98	26.99
ENALAPRIL MAL/HCTZ SMRY 0000 USA	enalapril/hydrochlorothiazide	17.17	26.99
UNIRETIC SMRY 1197 SWR	hydrochlorothiazide/moexipril	48.96	35.75
CAPTOPRIL/HCTZ SMRY 0000 USA	captopril/hydrochlorothiazide	13.49	15.00
FOSINOPRIL/HCTZ SMRY 0000 USA	fosinopril/hydrochlorothiazide	38.99	27.25
ZESTORETIC SMRY 0389 AZN	hydrochlorothiazide/lisinopril	19.98	39.99
LOTENSIN HCT SMRY 0594 NVR	benazepril/hydrochlorothiazide	32.98	39.2
MONOPRIL HCT SMRY 0400 BMP	fosinopril/hydrochlorothiazide	38.99	38.72
ACCURETIC SMRY 0300 PFZ	hydrochlorothiazide/quinapril	47.98	39.89
PRINZIDE SMRY 0289 MSD	hydrochlorothiazide/lisinopril	19.98	34.99
VASERETIC SMRY 0287 B5L	enalapril/hydrochlorothiazide	17.17	43.04
CAPOZIDE SMRY 0186 P.H	captopril/hydrochlorothiazide	23.98	34.55
CATAPRES TTS SMRY 0985 B.I	clonidine transdermal	14.00	61.00
GLYBURIDE/METFORM SMRY 0000 USA	glyburide/metformin	39.98	39.99
AVANDAMET SMRY 1002 GSK	metformin/rosiglitazone	164.13	95.99
GLUCOVANCE SMRY 0800 BMP	glyburide/metformin	39.98	59.99
METAGLIP SMRY 1002 BMP	glipizide/metformin	43.98	27.77
BISOPROLOL FUM/HCT SMRY 0000 USA	bisoprolol/hydrochlorothiazide	39.99	22.99
ATENOLOL/CHLORTHAL SMRY 0000 USA	atenolol/chlorthalidone	27.88	10.99
ZIAC SMRY 1193 BRR	bisoprolol/hydrochlorothiazide	39.99	67.83
TENORETIC SMRY 0884 AZN	atenolol/chlorthalidone	22.98	44.33
TIMOLIDE SMRY 1281 MSD	hydrochlorothiazide/timolol	26.98	22.00
NYSTATIN/TRIAM SMRY 0000 USA	nystatin/triamcinolone	12.99	7.99
LOTRISONE SMRY 0784 KPT	betamethasone/clotrimazole	18.98	61.57
PERPHENAZN/AMITRIP SMRY 0000 USA	amitriptyline/perphenazine	31.74	7.99
AMITRIPT/CHLORDIAZ SMRY 0000 USA	amitriptyline/chlordiazepoxide	28.98	35.99
LIMBITROL DS SMRY 0685 VLT	amitriptyline/chlordiazepoxide	28.98	70.99
SYMBYAX SMRY 0104 LLY	fluoxetine/olanzapine	234.99	245.78

Data sources

1. IMS Dataview - all Combination drugs sold in Retail
2. From Medicare Part D database www.medicare.gov –most common formulation of these drugs, retail price reported by Medicare reports and availability of generics by Medicare.
3. From Epocrates www.Epocrates.com (used by HMS and several MD's) drug composition, second source of retail price for formulation reported by Medicare, price of each component of the formulation, whether other drugs are available for the formulation.

Data gathering steps

1. Spreadsheet from IMS Dataview lists retail combination drugs sold.
2. Go to Medicare.gov and use the plan finder tool.
3. Enter that you do not have a current plan.
4. Get to the enter drugs section.
5. Enter the drugs in the spreadsheet.
6. Medicare identifies if generics are available – note in spreadsheet. Enter that you want most common dosage.
7. Go to plan finder.
8. Get drug detail.
9. This has a retail list price.
10. Enter price into spreadsheet.
11. Go to Epocrates.com.
12. Enter each drug into Epocrates.com.
13. Get the formulation from top right.
14. Enter into spreadsheet.
15. Identify the formulation that is given by Medicare.
16. If exact not found normalize e.g. if only 90 day – * 1/3 make a note if modified. Get the prices of each component for that formulation from Epocrates.com.
17. Make a note of it.
18. Epocrates.com will identify when there are multiple options available for each drug. Make a note of it (1 if proprietary 0 if there are multiple manufacturers) for each component.
19. Should match Medicare data.

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