

# The Drug Combination Competition

Companies are leveraging combinations of drugs and other products to gain competitive advantage and market share.

The development, commercialization, and utilization of drug combinations have skyrocketed in the United States. According to PharmaCircle research, the number of fixed dose combinations (FDC) approvals has more than tripled over the last decade compared to the early 1990s. Currently, there are numerous marketed FDCs and other combination regimens spanning multiple therapeutic areas, including infectious disease (HIV/AIDS, Hepatitis C, bacterial infections); oncology; endocrine disorders (diabetes, lipids); cardiovascular disease (hypertension, heart failure); women's health (contraception, menopause, osteoporosis); and respiratory diseases (asthma, COPD). According to an Oliver Wyman analysis, there were over 25 notable novel combination development programs underway in oncology alone in 2011.

Several factors have driven the dramatic escalation of combination products over the last decade:

**Greater scientific understanding.** Recent scientific advances have enhanced our understanding of the pathophysiology of HIV, cancer, and other complex diseases. Highly active antiretroviral therapy (HAART)—the use of at least three HIV drugs acting on different viral targets—reduces HIV replication, viral

resistance, patient mortality, and morbidity rates while improving quality of life. Similarly, increasing recognition that most cancers use multiple pathways to grow and proliferate has spurred development of entirely new classes of oncology agents, such as immunotherapies and targeted therapies, which are being combined to inhibit distinct pathway targets in order to improve treatment response while minimizing tumor resistance and side effects.

**Supportive regulatory and clinical environment.** Historically, the FDA and the US medical community were skeptical about drug combinations. However, regulatory policies and clinical thinking have dramatically changed over the last decade. The FDA established the “Office of Combination Products” in 2002 to evaluate combinations of drugs with other medicine products, such as devices and biologics. In 2004, the US government announced an expedited pathway for the FDA to review low-fixed dose combinations, co-packaged therapies, and single-ingredient HIV therapies for use by grant recipients of the US President's Emergency Plan for AIDS Relief. This past June, the FDA issued guidance for the “co-development of two or more new investigational drugs for use in combination” to address the rising number of novel combinations.

**Addressing public health threats.** FDCs are critically important for managing global infectious disease threats such as HIV/AIDS, malaria, and tuberculosis. The World Health Organization and other public health entities have encouraged the development of fixed-dose combinations which may improve adherence, reduce costs, and facilitate distribution in developing countries.

**Product differentiation opportunities.** With increasing brand competition, companies are eager to demonstrate better efficacy, safety, and convenience using a combination which is synergistic or additive. Companies competing in HIV, asthma/COPD, and diabetes have demonstrated higher efficacy rates with combinations versus single agents.

**Increased utilization.** Companies are pairing second- and third-line drugs with first-line products to enhance market access, earlier use, or preferred utilization. For example, many companies have combined their diabetes type 2 agents with first-line metformin, including Merck's combination of its best-selling brand Januvia with metformin to create Janumet.

**Leveraging the portfolio.** Companies increasingly are adopting a “multi-level competition” approach where they seek to win not only with a single brand but also across their product franchises and portfolios. Gilead Sciences wants to maximize sales of multiple HIV products to enhance its HIV franchise as well as with its new Hepatitis C (HCV) products to win with its overall anti-viral portfolio. Similarly, Roche bolsters sales of individual brands and its overall oncology portfolio by encourag-



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ing the use of combination regimens of its cancer agents.

**Extending the patent life.** Industry critics note that companies combine drugs nearing patent expiry with newer drugs with longer patents to extend the proprietary rights and marketability of the older agent. Some believe that Pfizer was using this “evergreening” strategy in its failed attempt to develop its powerful HDL-raising developmental agent torcetrapib only in combination with its best-selling, near patent-expiration agent Lipitor, instead of as developing it as monotherapy.

Combination drugs can be classified into two general categories: “combination drugs,” consisting of drug-drug combinations; and “combination products,” consisting of drug/non-drug combinations. A *combination drug* most commonly refers to a fixed-dose combination, a formulation including two or more active pharmaceutical ingredients combined in a single dosage form. However, companies may promote drug combination regimens which are not necessarily fixed dosed, such as co-packaged products or “free combinations,” two or more medicines with separate formulations and specific labeling for simultaneous use. Initially, fixed-dose combination drug products were developed primarily to target a single disease, such as Gilead’s anti-HIV FDCs. However, some FDCs target multiple diseases or conditions. For example, Pfizer’s Caduet is a FDC containing Lipitor to treat hypercholesterolemia and Norvasc to treat hypertension.

The FDA defines *combination products* as those which “combine different types of medical products, such as drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity.” Examples of combination products include a monoclonal antibody combined with a therapeutic drug; a device coated or impregnated with a drug or biologic such as a drug-

eluting stent; an orthopedic implant with growth factors; or insulin injector pens and metered dose inhalers.

### Competitive combination strategies

Pharmaceutical companies have leveraged combination products in a variety of ways to gain competitive advantages and enhance product sales:

#### Roche/Her2+ combination products.

Roche has been masterful in designing and executing winning drug combination strategies as exemplified by its fixed-dosed, free, and drug-conjugate combinations targeting patients with HER2+ breast cancer. For over a decade, Roche’s monoclonal antibody Herceptin combined with chemotherapy has been the mainstay of treatment for HER2+ metastatic breast cancer (mBC). Last year, the company launched Perjeta, a first-in-class HER dimerization inhibitor to be used in combination with Herceptin for mBC. Early this year, Roche launched Kadcyla, the first antibody-drug conjugate (ADC) for the treatment of HER2+ mBC. Roche is positioning Kadcyla—which contains Herceptin—to eventually replace Herceptin as a first-line mBC agent in combination with Perjeta and become the monotherapy of choice for second-line treatment of mBC. “Kadcyla is an antibody-drug conjugate representing a completely new way to treat HER2-positive metastatic breast cancer, and it helped people in the EMILIA study live nearly six months longer,” said Hal Barron, MD, Roche’s chief medical officer and head, global product development. “We currently have more than 25 antibody-drug conjugates in our pipeline and hope this promising approach will help us deliver more medicines to fight other cancers in the future.”

#### Gilead Sciences/HCV combinations.

Gilead is using a similar drug combination strategy to win in the HCV infection space as it did in HIV. Data presented in March demonstrated that a triple regimen of the HCV sofosbuvir, ledipasvir, and ribavirin produced a 100 percent response rate after 12 treatment

weeks for HCV genotype 1 patients. In June, the FDA granted priority review for Gilead Sciences new drug application for sofosbuvir, a once-daily oral nucleotide analogue inhibitor for the treatment of HCV infection in combination with ribavirin (RBV) as an all-oral therapy for HCV-infected patients with genotypes 2 and 3 and in combination with ribovarin and pegylated interferon for treatment-naïve patients with genotypes 1, 4, 5, and 6. Gilead is developing a sofosbuvir-ledipasvir coformulation that is being tested with and without ribavirin. FactSet Research Systems estimates that annual sales of sofosbuvir and its combinations will exceed \$6 billion and become the company’s biggest selling product by 2017.

**Teva/combination strategy.** Teva Pharmaceuticals, the world’s largest generic manufacturer, has announced that combination drugs and products represent an integral part of its new competitive strategy. Teva is pursuing “new therapeutic entities,” new formulations or combinations of older drugs, which would leverage Teva’s competitive advantages in generics, innovative specialty CNS drugs, and product formulation. For instance, Teva recently acquired Alexza Pharmaceuticals and its Staccato aerosol delivery system to serve as the platform for many new product combinations using already-approved drugs. In January, the FDA approved Alexza’s first product Adasuve, which combines the nearly 40-year-old anti-psychotic drug loxapine with the company’s new inhalation delivery device.

Scientific, clinical, regulatory, and commercial factors will continue to stimulate the development and utilization of drug combinations and shape the competitive landscape. Progressive companies will seek to preempt rivals by evaluating and developing their in-house drug candidates, identifying external drug and product combinations and partners, and by preparing insightful competitive strategies to win the drug combination competition. 