

Fixed-dose combination

The advantages and challenges of fixed-dose combination products: Considerations for design, formulation, manufacturing and analysis

The many advantages of fixed-dose combination (FDC) drug products have made them an increasingly attractive option for patients, pharmaceutical companies, physicians, and regulatory agencies. These potential benefits include, but are not limited to, better patient compliance, more convenient dosing associated with improved clinical performance, cost savings for both patients (fewer co-pays) and drug manufacturers (reduced production costs), and extended patent protection and market positioning in the face of competition from generics. These advantages cannot be taken for granted, however. Producing safe and effective FDC products that are also cost-effective and have a high probability of a regulatory approval requires thoughtful product design, access to state-of-the-art formulation and manufacturing technology, and advanced analytical tools.

Introduction

Understanding both the significant competitive advantages that FDC products can offer and the difficulties and potential pitfalls associated with development and manufacturing of FDC drugs in oral solid dosage forms is a critical first step for companies exploring this approach. Recognizing that cost savings, lower risk, and accelerated timelines can be achieved by partnering with a CDMO that has a proven track record of successfully producing FDC products is an important next step. Cambrex has collaborated and partnered with pharmaceutical customers to develop and manufacture FDC drugs that are US FDA approved and are currently in the various stages of clinical development. The experience, know-how, and team of skilled experts that Cambrex brings to these partnerships, combined with its wide range of specialized equipment and technological competencies, ensure the production of high quality FDC drug products that meet their clinical endpoints and receive final approvals from regulatory agencies.

Over the past decade, we have established a vast knowledge base in the area of FDC drugs. Cambrex continues to expand our formulation and manufacturing capabilities through collaborative agreements and by bringing on-stream specialty equipment to enable the production of FDCs. Some examples include hot melt extrusion, wet granulation/roller compaction, extrusion-spheronization, and fluid bed technology. These manufacturing capabilities provide greater flexibility for our clients in terms of a variety of manufacturing platforms for the production of FDC oral solid dosage forms. These choices include multi-layer tablets, mini-tablets that can be compressed together or combined in capsules, sachets, or stick



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FDC products offer significant advantages for the pharmaceutical industry, including the potential to extend protection of patents and market share, reduce overall manufacturing costs, and add new NDAs to a company's drug development portfolio with shorter and less costly paths to regulatory approval.

About Cambrex

Cambrex is a leading global contract development and manufacturing organization (CDMO) that provides drug substance, drug product, and analytical services across the entire drug lifecycle.

With over 40 years of experience and a growing team of over 2,200 experts servicing global clients from North America and Europe, Cambrex is a trusted partner in branded and generic markets for API and finished dosage form development and manufacturing.



packs, and microparticulate systems filled into capsules. Cambrex also offers a variety of polymer-coating options to enable controlled release of the different drug substances in an FDC product. Cambrex also has hands-on experience in taste masking that relies on ion exchange technology.

More FDC products flowing into pharma pipelines

The numbers tell the story. Pharmaceutical companies – and the FDA – are embracing FDCs. From 1990 through 2013, the FDA approved 131 FDC products, on average 5.7 per year, the largest number targeting indications related to cardiovascular disease, followed by endocrinology products and treatments for infectious diseases.¹ Of those 131 approved FDCs, 98 were oral dosage forms.

Between 2010 and the end of 2015, of the 655 New Drug Applications (NDAs) approved by the FDA, 63 were for FDCs.² This represents nearly 10% of the NDAs approved during that 5-year period and, on average, 12.6 new FDC products per year. As the numbers of FDC products in

FDC products can extend patent life and market dominance

For pharmaceutical companies, FDC products represent an attractive strategy to gain additional patent protection and market exclusivity for a drug approaching patent expiration. “In the US, if an FDC is novel, nonobvious, and useful, it can be patented and the exclusion of competitors from the market can be enforced.”³ Further, “The FDA provides three years of market exclusivity to new [new molecular entity] NME-FDC when the application contains new clinical investigations. If the new FDC is not patentable, the patent and exclusivity life of the FDC will typically be equal to the three year market exclusivity or the longest patent and exclusivity life of the individual components.”³

Cambrex et al. compared the effective patent and exclusivity life of FDCs with that of single active ingredients from 1980 through 2012.³ The FDA approved 28 FDC products containing a NME and 117 FDC products containing only already approved products during the study period. Overall, FDC products without a NME added a median of 9.7 years of patent and market exclusivity protection to that of the single active ingredients. When the company producing the non-NME-FDC was also the sponsor of the single ingredient drugs included in the combination, the non-NME-FDC added a median of 7.73 years; whereas, if those companies differed, the non-NME-FDC added a median of 11.48 years of patent and market exclusivity protection.

development and coming to the market increase, the pharmaceutical industry is looking to FDCs as a promising strategy to repurpose, repackage, and expand indications for existing and novel therapeutic agents. The potential to extend the patent life and market exclusivity of a company’s APIs is a potent financial incentive.

Improved convenience and safety

Among the numerous advantages FDCs offer patients, physicians, and pharmaceutical companies, several are particularly noteworthy. One of these is convenience. For patients affected by diseases that require treatment with multiple medications, replacing two or three pills with a single pill can substantially reduce a patient’s pill burden. Examples include hypertension (often treated with a combination of beta blockers, ACE inhibitors, and diuretics), diabetes, HIV and other viral infections (typically treated with multi-drug cocktails), cholesterol disorders, and cancer. Pain management is another therapeutic area in which FDCs are gaining increased attention. An emerging strategy combines an opioid drug with an opioid antagonist to counter the “high” brought on by the opioid. This approach achieves effective pain relief, but with a reduced risk of addiction. In addition, FDCs can be used to develop abuse deterrent formulations (ADFs).

FDC products comprise multiple drug substances that are taken in a single dose. The components of an FDC cannot be changed or separated. A physician can prescribe more or less of the combination product, but the ratio of the individual drug components cannot be altered. As a result, FDC products may help prevent medication errors and enable better control of dosing. Dosing is not left up to physicians; it is built into the FDC product and based on clinical trial results.

The goal of combination drug treatment is not only the delivery of two or more therapeutic agents that have different mechanisms of action. FDC products can also take advantage of potential synergistic effects between the individual drug substances, which could improve overall effectiveness and perhaps allow for simplified and reduced dosing, which may lower the risk of adverse effects.

Cost savings

A decreased pill burden is only one example of how FDCs are more convenient for patients. Replacing two or three pills with a single FDC drug product also translates into less time spent filling (and refilling) prescriptions. With an FDC product, physician offices also have fewer prescriptions and renewals to process. Taking this a step further, fewer prescriptions means fewer co-pays for patients, saving them money. Theoretically, at least, pharmaceutical companies should also be able to save money producing a single-dose FDC product, compared to what it would cost to manufacture, package, and market two or three individual drugs.

Accelerated regulatory pathway

Furthermore, compared to the cost of developing a new API, substantial savings can be realized when developing an FDC comprised of previously approved new chemical entities or their generic counterparts. The FDA allows for an abbreviated clinical development program that can speed the path to approval if sufficient drug safety and tolerability data and supporting efficacy data are already available. Companies can save valuable time and resources as well by taking advantage of the FDA's 505(b)(2) approval pathway.

Over the past several years, many approved FDC products have used the 505(b)(2) pathway. In more than half of those cases, the companies still had to perform at least some Phase II and III clinical studies.⁴ Specifically, about two thirds of the FDCs approved using the 505(b)(2) route have required at least one Phase II or Phase III study, and approximately one-third needed more than four Phase II/III studies.⁴

Examples of FDA-approved oral solid dosage form FDC products that greatly reduce the pill burden for patients with HIV infection are:

- Gilead's Genvoya (elvitegravir 150mg/obiciclat 150mg/emtricitabine 200mg/tenofovir alafenamide 10mg)
- Viiv Healthcare's Triumeq (abacavir 600mg/dolutegravir 50mg/lamivudine 300mg)

An updated European Medicines Agency (EMA) guideline on the clinical development of FDC drugs is expected to be issued during the fourth quarter of 2017. It details the evidence that companies need to present to support authorization of FDCs that contain two or more already approved or new active substances, whether small molecule drugs or biologics.⁵ Initially adopted in March 2017, the newly revised EMA guidelines require data to "support the rationale for combined use of the active substances." Simply providing previous evidence of combined use "will not suffice to establish the positive benefit/risk of the combination."

The EMA states: "Specific considerations apply for fixed combination medicinal products where the active substances have different - but related - therapeutic indications and different pharmacological targets, e.g. a fixed combination medicinal product for treating patients at high cardiovascular risk containing a lipid-modifying agent and an antihypertensive agent. A relevant contribution of all active substances and existence of a positive benefit/risk for these fixed combination medicinal products should be documented." Furthermore, "as a minimum requirement, in the absence of clinical trial data studying the specific free active substances used in combination on clinical outcome, the potential for PK and

PD interactions should be established to understand if the effect of the individual active substances may be modified by their combination. Usually, PK data (a DDI study) will suffice."

Developing and manufacturing FDCs factors to consider

At the outset, when designing an FDC drug, API selection is the foundation on which creating a successful product rests. Selecting the APIs to include in a two-drug or three-drug FDC product should focus on maximizing the benefit-to-risk ratio by identifying combinations that have the potential to improve efficacy while avoiding any new safety or tolerability issues. Key drivers for pharmaceutical companies include the ability to repurpose already approved therapeutic agents with a low risk of toxicity, to combine and repackage drugs commonly prescribed together, and to pair their APIs with popular off-patent drugs or generic compounds.

Collaboration with ExxPharma Therapeutics

Hot melt extrusion is a technique used to enhance the solubility of drug substances. Cambrex entered into a collaboration with ExxPharma Therapeutics LCC, a pioneer in HME, to apply the technique in the development and manufacturing of drug products. The aim of HME is to minimize exposure of a drug substance to elevated temperatures during manufacturing - temperatures above a drug's melting point that could lead to degradation. HME may offer the advantage of higher drug loading versus a spray-dried dispersion containing the same API. This is particularly useful in an FDC where higher drug loading may be necessary. HME also helps ensure the stability of a drug substance by eliminating air during melt extrusion, thereby limiting oxidative degradation.

HME technology offers additional advantages as well as:⁶

- Small footprint of the extruder
- Process uses no organic solvents, is continuous, and is easily scalable
- HME does not require an extra densification step
- Unlike with spray-dried solid dispersion technology, the material generated can be blended directly with other FDC components and compressed into tablets

The use of HME to produce FDC drug products simplifies technology transfer and scale-up, accelerating the time to market, and contributes to improved overall product quality.



Important factors to consider in designing an FDC product include the following:

- Differing pharmacokinetic and target release profiles of the component drug substances
- Physical and chemical compatibility of the APIs
- The target patient population (age, severity of illness and/or disability)
- The full range of oral solid dosage form options
- Total development and production costs, including formulation, manufacturing, and packaging

Working with a CDMO partner

Theoretically, at least, there should be a cost advantage in the production of a single FDC drug compared to the costs of manufacturing, analyzing, testing, packaging, and marketing two or three individual products. However, the need for specialized equipment and advanced methods and technologies across the formulation, analytical, and manufacturing workflows in order to produce these more complex combination dosage forms can increase capital equipment costs. Outsourcing FDC product formulation and manufacturing, and partnering with an experienced CDMO that has the infrastructure, capital equipment (and competency to run said equipment), technology, and skilled personnel can reduce the costs – both capital (capex) and operating (opex) expenses – and the risks associated with creating high quality FDC products.

The main challenges in FDC product development, which a knowledgeable CDMO partner can help overcome, include the following:

- Designing a stable formulation
- Optimizing the bioavailability and delivery of the individual drug substances
- Understanding the potential for – and avoiding – unwanted interactions and interferences between the API components
- Acquiring the necessary capital equipment – investment of millions of dollars in new equipment required for production of an FDC product

Access to Cambrex's wide range of formulation and manufacturing technologies allows our sponsor partners to identify the most appropriate, efficient, and cost-effective development approach for any particular FDC product. Cambrex can apply all of its technologies and approaches from development scale (500g) through to full-scale commercial manufacturing. This high degree of flexibility, combined with ease of access to the equipment and technological resources all in one location, not only helps ensure a productive and highly collaborative partnership, but also allows Cambrex to offer aggressive timelines, with on-time delivery.

Cambrex's specialized equipment and techniques include bilayer presses, wet granulation/roller compaction, fluid

bed technology, solvent pellet layering, and extrusion-spheronization. Through a partnership with ExxPharma Therapeutics, Cambrex offers hot melt extrusion (see "Collaboration with ExxPharma Therapeutics") to improve manufacturing of drugs with poor solubility. Using innovative formulation development and cutting-edge manufacturing technology, Cambrex can create solid dosage forms that include multi-layer tablets, tablet-in-tablet configurations, mini-tablets, and microparticulate systems. Mini-tablets can be combined in capsules, or packaged into sachets or stick packs for resuspension and use in pediatric delivery systems. Similarly, microparticulate systems of individual APIs can be combined in various dosage forms and strengths for adult or pediatric dosing.

Cambrex can use a range of polymer coating techniques to segregate FDC product components that may be incompatible and to provide sustained- or delayed release control of component APIs. Traditional sugar and polymer-coating methods and Cambrex's novel ion exchange technique offer a range of effective options for taste masking.

Cambrex has in place a full range of analytical capabilities to develop and validate stability-indicating methods for final release of an FDC product. One commonly used technique is ultra-high pressure liquid chromatography (UPLC), which is very effective in separating actives and their respective related substances. The ability to use a single analytical method to obtain the necessary data reduces the time and cost associated with generating final or stability quality control (QC) results.

Finally, from a regulatory perspective, Cambrex's strong record of collaborating with pharmaceutical companies to bring FDC products to the market includes the knowledge and experience in gathering and preparing the data and accompanying analysis and reports needed for regulatory filing.

Conclusions

A recent case study describing specific projects that Cambrex completed for two large pharmaceutical customers demonstrates the broad-ranging technological capabilities and expertise Cambrex can offer.⁷ In one collaboration, Cambrex developed and manufactured a complex three-API FDC product in which one of the APIs was incompatible with the other 2. In the second project, the challenge involved combining 2 APIs with different release profiles. These examples, and the creative solutions Cambrex was able to deliver using multi-layer tablets, mini-tablets, and polymer-coating technology, exemplify the novel types of FDC products on the market and in development that offer important advantages for patients, physicians, and the pharmaceutical industry.



References

1. Kararli TT, Sedo K, Bossart J. Fixed-Dose Combination Products — A Review (Part 2 – Analysis). April 1, 2014. Drug Dev & Delivery Available at www.drug-dev.com (last accessed August 2017).
2. Kwon KC Lee C. Analysis of Fixed-Dose Combination Products Approved by the US Food and Drug Administration, 2010-2015. Implications for Designing a Regulatory Shortcut to New Drug Application. Ther Innov & Reg Sci 2017; 51:111-117
3. Hao J, Rodriguez-Monguió R, Enrique Seoane-Vazquez E. Fixed-Dose Combination Drug Approvals, Patents and Market Exclusivities Compared to Single Active Ingredient Pharmaceuticals. PLoS One 2015; 10(10):e0140708.
4. King J. Fixed-Dose Combination Products — Navigating the Combination Rule. March 22, 2017 blog post. Available at www.camargopharma.com/2017/02/fixed-dose-combination-products-navigating-the-combination-rule/ (last accessed August 2017).
5. European Medicines Agency. Guideline on Clinical Development of Fixed Combination Medicinal Products. Available at www.ema.europa.eu/contact (last accessed August 2017).
6. Terefe H. The Origins of HME as a Solubility Enhancement Manufacturing Technology. Available at: www.americanpharmaceuticalreview.com/Featured-Articles/341249-The-Origins-of-HME-as-a-Solubility-Enhancement-Manufacturing-Technology/ (last accessed August 2017).

