

Making a Case for a Fixed Dose Combination Drug Strategy

Over the past two decades, pharma's acute focus on the patient has driven great innovation and investment in ways to deliver active pharmaceutical ingredients (APIs) in finished drug products. Oral administration is the most convenient method of drug administration for patients due to the ease and flexibility of dosing. This makes it the route preferred by health care providers and drug developers.¹

Every aspect of the dose and formulation – color and size, taste and texture, controlled release, and dosing frequency – can have an impact on therapeutic performance, which can affect the ability of the finished drug product to optimally treat the condition and the patient.

Fixed dose combination (FDC) drug products are an oral solid dose (OSD) platform steadily gaining favor. Fixed dose combinations are defined by the World Health Organization (WHO) as a combination of two or more APIs in a fixed ratio of doses and in a single dose form.²

FDCs offer several potential advantages to patients and developers including:

- Better pharmacokinetics and therapeutic synergies
- Simplified therapeutic administration and dispensing
- Reduced therapeutic polypharmacy
- Improved patient compliance

Other tangible benefits derived from combining therapeutics into a single OSD further support the FDC business model. From a Cost-of-Goods (CoGs) perspective, commercial FDC drugs are more efficient to manufacture, distribute, and dispense than two or more finished dose forms.³

A Practical Strategy for Improved Patient Compliance

Popularity and demand in the FDC market stems primarily from patient centricity because FDCs can improve patient compliance due to convenience of administration.

A systematic review of 21 studies including information on 27,230 subjects showed better compliance and therapeutic effect among patients receiving FDCs. According to the study, these findings were consistent with data from observational cohorts. The review's authors noted a tendency towards greater virological suppression among patients receiving FDCs in randomised trials and observational cohort studies. In all studies reporting patient preference, FDCs were preferred. The study concluded that FDCs offer multiple advantages for programs and patients, particularly with respect to treatment adherence.⁵

The impact of prescription non-compliance on the overall cost of health care to society is well documented. When patients take their medications as prescribed, statistically their health outcomes improve. When patients fail to comply with doctors' orders, health outcomes are more often poor and increase the potential for more costly types of care including hospitalisation and surgery.

Recent studies examining the cost of patient non-compliance in the US put the figure between \$100–\$289 billion annually in increased healthcare costs. In addition, the lost productivity due to patients being sicker and debilitated potentially multiplies the total increase in health care costs by 2.3 times.⁶ Fewer pills per patient can help suppress the overall cost of patient

care. When the patient group is large, the potential for cost savings can be significant.

Efficient Development Pathways Using FDCs

FDCs are becoming more widely accepted because they offer developers a practical and more economical path for developing first- and best-in-class therapies.² Although similar development to traditional monotherapies is involved, the presence of two or more APIs requires additional analysis including drug-drug interactions and dose-ranging studies to determine optimal API loads and ratios, which add to the complexity of FDC development.

In practice, the above has driven FDC product developers away from combining two or more new chemical entities (NCEs) and towards developing combinations of previously approved, well-understood APIs. About 99% of FDC products approved in the past 20 years or more include at least one previously approved API where it is possible to leverage established clinical and patient data.⁴

This enables developers to focus solely on obtaining the data they need to demonstrate the safety and efficacy of the proposed FDC to regulators. Added to this is the option for FDC drug product developers to utilize the FDA's 505(b)(2) approval pathway, providing a fast-track clinical development route,



significantly accelerating time to market for FDCs.

Technologies and Methodologies Ready to Close Gaps in FDC Business Model

Two things support the success of any commercial OSD pharmaceutical product:

1. Timely, cost-efficient development path to regulatory approval. Drug-drug compatibility studies and detailed risk assessments are particularly important to support timely FDC regulatory filings.
2. A robust manufacturing strategy to deliver quality product to patients and markets.

Despite the obvious advantages FDCs offer all stakeholders, due to the challenges associated with formulating and manufacturing combined drugs, analysts noted that year-over-year the overall growth in the number of FDCs being commercialised was not as significant as one might expect.³

With increased access to advanced OSD processing technologies and drug-drug interface studies, combined with specialised equipment experience from pharma's manufacturing partners, this potential "growth gap" in the overall business case for FDCs is fast closing. In a broad and sustained response, pharma's manufacturers, along with pharmacologists, equipment and excipient suppliers have continued to innovate new solutions to overcome issues formulating FDCs.

The pharma industry now has access to an impressive list of highly mature processing techniques and enabling technologies that are perfectly suited to doing the heavy lifting when it comes to processing drug substances into finished OSD forms. For OSD developers, it is likely a familiar list:

- Wet granulation
- Dry granulation
- Blending
- Spray drying
- Hot-melt extrusion
- Spheronisation
- Tablet compression
- Coating

Although the above list of enabling technologies may not be perfectly complete, deftly applied, the methods provide significant latitude in controlling and managing the pharmacokinetic properties of small-molecule APIs *in vivo*. From creating amorphous solid dispersions (ASDs) to multiple-unit particulate systems (MUPS),

pharma now has general access to key technologies that are more capable than ever to support the business case for FDCs. These established systems and process knowledge have proven highly capable in developing FDCs using pre-existing manufacturing capability.

Contract Development & Manufacturing Organizations (CDMOs) Ready to Support FDC Innovation and Development Growth Now

Developing any drug successfully involves risk, which is balanced against the potential reward from the program. Because the FDC concept is so patient-centered and features existing therapeutically beneficial compounds, development paths become less financially risky. Development paths are more predictable, even though developers must deal with the added complexities associated with formulating two APIs or more into a single dose. However, the impact of those complexities reveals another potential gap in the FDC business case – where to access the experience and enabling technologies required to develop these drugs successfully?

To fulfill their FDC drug development strategies, pharma innovators are accessing key critical enabling technologies and capacity in a variety of ways. For a growing segment of pharma, it makes clear business sense to engage fully capable external partners to execute their drug programs expertly and cost-efficiently. The rise of the CDMO industry is predicated on that fact. Considering FDC's commercial and patient potential, an FDC program developed with expert commercial partners is likely to be better able to generate the anticipated return whilst driving continuous innovation in OSD.

Because the molecule will always dictate how the drug product is ultimately processed, engaging CDMOs, experienced in developing robust processes to combine and formulate FDCs makes good sense for business and patients.

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