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WHITEPAPER

Fixed-dose combination drugs: Innovative formulation and development strategies for bringing best-in-class products to market

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Executive summary

The development of fixed-dose combination (FDC) drugs plays an increasingly important role in lifecycle management strategies for mature drug products. It also offers the potential of getting safe, effective therapies to patients more quickly via shortened clinical development programs, reduces manufacturing costs, and improves patient compliance through more convenient dosing and lower costs, which in turn can improve clinical performance. These collective benefits are hard-earned, however.

Successful development of FDCs requires a systematic, risk-based strategy based on a thorough understanding of the chemistry, mechanism of action, and pre-formulation characteristics of each active pharmaceutical ingredient; analytics capabilities to assess the compatibility of the active ingredients, screen for possible drug-to-drug interactions, evaluate drug stability, and determine dose differential; innovative approaches to drug formulation and manufacturing to overcome compatibility challenges; and regulatory insight and expertise to navigate the sometimes tricky route to approval.

This whitepaper will discuss the key considerations for establishing a robust oral FDC drug program, focusing specifically on the following resources:

- Advanced analytic tools for predicting drug synergism or antagonism
- A decision support tool to guide formulation choices for optimal drug performance and stability
- Primary production options suited to common physiochemical properties that require manufacturing accommodations
- A list of key regulatory requirements and guidelines for drug registration

By applying the foundational strategies discussed herein, sponsors can successfully develop and commercialize FDCs to bring effective treatments to patients and maximize the value of branded products.

Introduction

Fixed-dose combination (FDC) drugs combine two or more active ingredients in a single dosage form, offering patients, prescribers and drug sponsors a host of potential advantages. Patients may benefit from enhanced therapeutic efficacy via drug synergy, a reduced side effect profile, and improved treatment compliance (via reduced pill burden, reduced dosing frequency, less hassle and potentially lower cost). These factors also make FDCs appealing to prescribers, who can simplify the drug regimen of their patients and potentially increase effectiveness. The benefits to sponsors include also extension of patent life of the active ingredients and a chance to counter the impact of generics, rounding out lifecycle solutions for a company pipeline. In addition, FDCs can expand a company's patient base by exploring novel indications for their existing drugs, alternative pricing options, and new business opportunities.

These factors explain the widespread popularity of FDCs. Currently, more than 400 FDCs are approved in the U.S. and approximately 200 are on the market in India and Europe. New development is also healthy, with about 45-50 approved per year in the U.S., primarily for small molecule combinations in oral formulations. The most popular indications include metabolism and endocrinology, genitourinary, anti-infective, cardiovascular, respiratory, and neurologic, with far fewer FDCs on the market in immunology, oncology, and hematology. This may partly reflect the larger number of monotherapy drugs on the market in some of these indications as well as the longer history of approved monotherapies, which has made it easier to identify compatible combinations over time. With larger portions of the population in need of these classes of drugs—as with diabetes and heart medications, for example—there has also been great opportunity to repurpose and explore applications of these drugs beyond their initial target indication.

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Key challenges in FDC development

While there are numerous advantages to FDCs, their development can present unique challenges compared to individual drug development. The majority of these roadblocks fall into four primary categories, aligned with stages of FDC development:

- Identification of candidates that may be physically and chemically compatible and synergistic
- Formulation to accommodate compatibility and delivery requirements
- Manufacturing to address formulation needs and enable stable storage
- Documentation for regulatory bodies that demonstrates the safety, efficacy, and appropriateness of the FDC

As sponsors consider the best approach to FDC exploration and development, challenges will undoubtedly arise in selecting the best drug candidates, perfecting the formulation, choosing production processes, and conducting the appropriate clinical research and documentation work to justify market approval. In this whitepaper, we provide strategies and solutions to support sponsor decision-making for many of the common roadblocks on the journey through oral FDC development and approval.

Advanced analytics can identify promising FDCs

In order to create effective FDCs for patients, the drug combination must be stable and safe. This requires compatibility both in terms of the drugs' physical properties and chemical characteristics. A large portion of the initial phases of FDC development is devoted to assessing compatibility with the goal of identifying problems as early in the development process as possible. Although physical compatibility concerns can often be addressed with manufacturing and formulation techniques, clinical incompatibility is challenging and expensive to address after initial manufacturing, so spending the time and effort upfront is a good investment.

Advanced analytics can help ensure the best return on that investment. Enabled by computerized mining of detailed drug databases, artificial intelligence-based analytics capabilities such as machine learning or "deep" learning, neural network technology, and network-based modeling can search for potential pharmacologic, biologic, genetic, or other points of drug-drug synergy or antagonism. Potential impurity formation, chemical interactions, interactive mechanisms of action, degradation, moisture concerns, and other critical considerations can be predicted before the drugs are even placed side by side in the lab. Multiple studies examining applications of these techniques and tools have found that they can accurately identify effective as well as problematic combinations.

Examples of these databases and technologies include:

- CoSynE or "Combination Synergy Estimation," a machine learning tool to identify new and likely safe drug combinations for novel therapeutic and even personalized medicine approaches
- The INDIGO algorithm (INferring Drug Interactions using chemoGenomics and Orthology), which effectively identifies the genetic components underlying drug function and predicts their combined impact
- The National Cancer Institute's ALMANAC database (A Large Matrix of Anti-Neoplastic Agent Combinations) for drug combination identification in oncology
- DeepSynergy, a machine learning software created by Austria's Institute of Bioinformatics, which shows high predictive ability for drug interaction identification

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While not every drug is part of these databases, numerous options exist for companies wishing to digitally pre-screen for potential FDC options or to learn more about their desired combination in advance of scientific testing in the lab. These tools offer analytically rigorous predictions based on large, detailed aggregations of data, and can provide opportunities for product life-cycle management. Specifically, they can identify potential indications or FDCs to consider for existing products in a company portfolio. These technologies can typically screen for combinations with existing approved molecules and generics as well as by release profile and other target usability features. By identifying potentially effective combinations or indications, digital analytics can expedite time to market for novel therapies, benefiting patients and patent holders.

Similar screening work can be done by experts in pharmacology by examining the characteristics of pre-identified drugs under consideration for combination, evaluating and comparing them based on known areas of import.

Prior to laboratory and clinical testing, chemical compatibility screening (digital or otherwise) should consider:

- Target release profiles
- Dosage
- Delivery method
- Adverse event (AE) profiles
- Molecular targets
- Pharmacokinetics and pharmacodynamics (PK/PD)
- Patient population characteristics
- Common polypharmacy profiles for patients with the target indication

Physical and chemical compatibility can be further studied using ASAPprime® (Accelerated Stability Assessment Program) stability modeling or a traditional stability analysis program. These considerations help identify whether the drugs may interact both in and outside the body, highlighting any potential concerns for storage and manufacturing as well as clinical use.

Decision support simplifies FDC formulation selection

Once a promising FDC is identified and preliminary screening suggests that the combination will not generate excessive toxicity or AEs, the next challenge is formulating the combined drug product.

A best-case scenario involves chemically compatible drugs of similar weight and dissolution/release profiles, in which case a standard, monolayer tablet or capsule provides a simple solution. In many cases, however, chemical incompatibilities or diverse release profiles, storage requirements, or drug volumes require creative manufacturing approaches and layered or innovative combination practices.

The below decision tree offers preliminary guidance toward formulation options based on chemical properties.

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Decision tree for formulation design of a fixed dose combination (FDC)

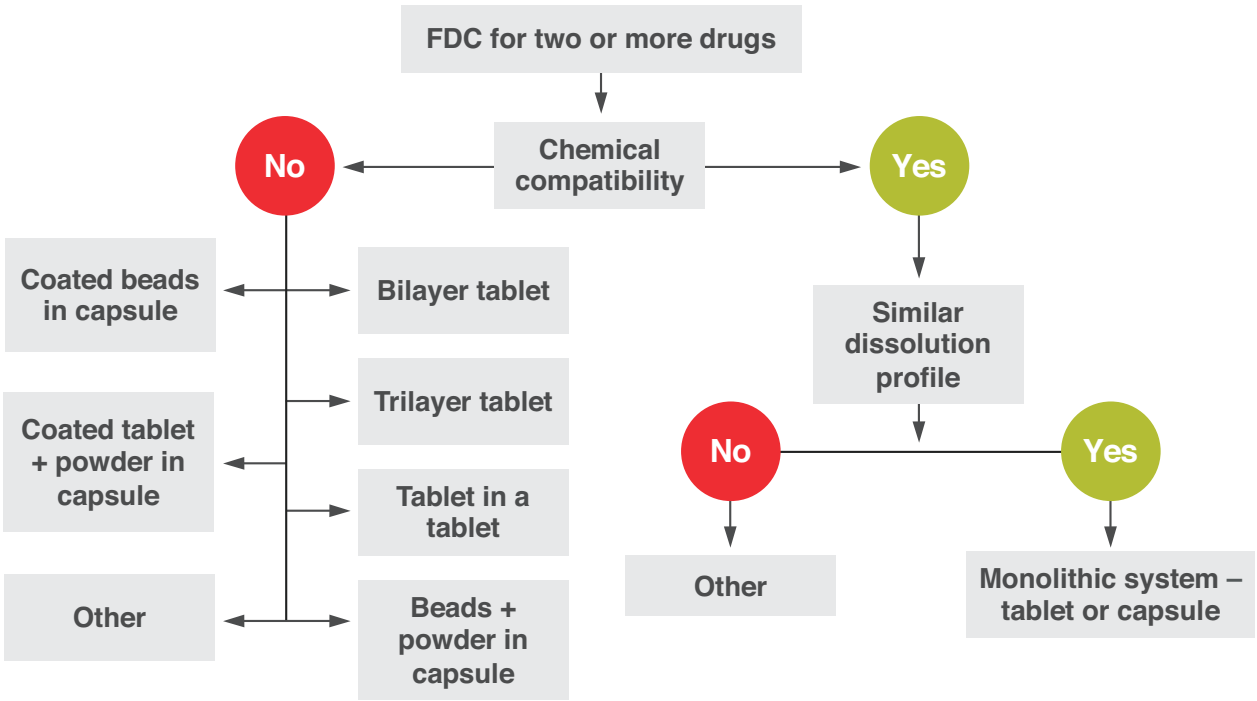

Table 1

Oral FDC formats	Design features	Considerations
Monolayer tablets	Physical blend of the active pharmaceutical ingredients (APIs), formed and pressed into a uniformly distributed tablet	For drugs compatible at surface level and in physical properties
Powder or granule blend in capsules	Physical blend of the APIs as powder or granules, together in a capsule	For drugs compatible at surface level and in physical properties
Bilayer tablets	FDC containing two APIs, or an immediate release layer together with a controlled release layer, in a tablet dosage form	Requires surface compatibility but enables differential release characteristics and minor dose differentials
Trilayer tablets	FDC or an immediate release layer plus a controlled release layer separated by a middle placebo layer in a tablet dosage form	Placebo layer extends shelf life by separating drugs that are not compatible at a surface level due to migration of moisture or other chemically incompatible ingredients
Multiparticulates	Beads, pellets, or mini-tablets as controlled release forms or FDCs filled in capsules	Each API is made separately and then filled into capsules as different components, enabling unique formulation properties
Tablet-in-tablet	FDC of two APIs, with one in a core insert tablet form and the other in the outer core	Useful for APIs with different release requirements and dose differentials

The outcomes of analytics, in vitro, and bioequivalence studies all play a role in selecting the right final FDC solid dose format (Table 1) and ensuring the proper delivery of each active pharmaceutical ingredient (API) in the product. The following factors related to dosing, stability and release profile for the individual and combined APIs must also be considered:

- Dose differential
- Forced degradation
- Excipient compatibility
- Solubility and in-vitro dissolution profiles
- Existing approved dosage formats of individual drugs
- Maintenance of the dissolution/release profile of individual drugs to justify equivalence
- Analytical results for potency/impurities/dissolution of the drugs once combined

In some cases, drug properties prevent simple combinations in layered tablets as well as the standard workarounds and troubleshooting or new technique development is necessary to maintain bioequivalence and degradation stability for regulatory requirements. In other cases, physical challenges—such as significant dosage volume differentials—require extra testing to ensure tablet uniformity and potency can be maintained during production. Provided proper testing is done throughout early formulation and manufacturing efforts, many desired drug combinations can be suitably united through standard or creative formulation solutions.

Process requirements inform manufacturing decisions

When the physical and chemical properties of the components are understood, it is possible to select manufacturing processes appropriate for the end product. Although regulatory agencies often require that the FDC has been clinically tested, in some cases, early-phase research begins with the two drugs given separately. Provided preliminary data look promising, the FDC and final manufacturing work is done prior to moving into later-phase studies.

Selection of a manufacturing process must account for the critical physicochemical properties of the components both alone and combined. Uniform, compatible APIs can typically be blended together and formed into a standard tablet or made separately and compressed into a bi- or tri-layer tablet. Ingredients requiring different levels of moisture control may be developed separately, with a moisture barrier encapsulation process for the more sensitive API and one of a variety of combination techniques for the final product.

Table 2 provides basic descriptions of the primary manufacturing options for oral formulations, as well as some of the API properties they accommodate. Adjustments to other manufacturing parameters, such as speed of mixing, compression, and solubility, can alter the final product and address physical or chemical concerns identified during analytics.

Table 2

Drug production techniques	Process features
Co-granulation or separate granulation • Dry • Wet • Fluid Bed	Depending on the properties of the APIs, each component may require wet, dry, or fluid bed creation of granules. This involves the transformation of fine powdered drug into granules that are dust-free, easy to work with, and easy to compress. Each process must be carefully studied to ensure post-granulation products are uniform in their content, hardness, moisture, compression, porosity, density, size, and more will meet the final product's requirements.
Extrusion-spheronization	This method of pellet creation starts with wet granules that are shaped into cylinders, then rounded into spheres and dried. In turn, these can be compressed into tablet layers, cores, or beads to address large dosage differentials and release requirements.
Drug layering	Layers are created to hold an API together and can be formed using sprayed liquid solutions, suspensions, or dry powders.
Encapsulation • Single blend, population of beads, or pellets • Multiple population of beads, pellets, or mini tablets	Stable drugs may be mixed together as a uniform blend of powder, beads, or pellets and then encapsulated. To avoid stability challenges, drugs that cannot be directly combined may undergo process staggering with separate granulation, compression, or encapsulation with multiparticulates. The end product is a capsule containing a mix of beads, pellets, or mini tablets of the different drugs.
Tablet compression • Single layer • Multi-layer • Tablet-in-tablet	Tablets with multiple layers often require multiple compression processes, and in many cases, a coating for each layer. The layers are mixed and compressed individually and can control release times as well as inhibit instability during drug-on-drug contact. Single-layer tablets have the stable components fully blended with matching release profiles.
Coating • Active • Cosmetic	Coatings can serve active therapeutic purposes, such as control of release profiles and prevention of degradation or the formation of impurities. They can also provide moisture barriers for APIs with different properties and storage requirements. Cosmetically, coatings can mask odor or flavor and improve aesthetics.

Table 3

FDCS NDAs: Key elements to address	

Clinical rationale for combination	Co-granulation or separate granulation
	• Summary or rationale for clinical use, to include reference to:
	  • Prior IND/NDA details for initial innovations
	  • Other sponsors' IND/NDA (right to obtain for reference)
	  • Published literature, clinical studies and other data
	• Treatment guidelines
	• Prior FDA findings of safety and efficacy

Clinical pharmacology and biopharmaceutics components	• Bioequivalence studies
	  • PK/PD profile of individual components and combined product
	  • Risk profiles
	• Bioanalytical method validation
	• Summary of food effect considerations
	• Dissolution testing
	  • Multimedia dissolution in vitro for FDC vs single ingredients
	  • Release profile(s) and documentation of solubility, bioavailability, solidity in the gastrointestinal tract

Chemistry/ manufacturing components	• Quality standards for each active ingredient and dosage form
	• Stress studies
	  • (Lack of) interaction between ingredients
	• Drug release information (dissolution)
	• Stability data
	  • Long term and short term under high temperature and/or humidity
	  • Packaging considerations if necessary
	• References/data supporting excipients
	• Manufacturing processes for active ingredients and dosage form

Depending on the circumstances, new manufacturing challenges may arise when formulations are combined, while existing concerns may be eliminated. For example, the physical combinations of desired formulations may produce dose-related weight imbalances which must be adjusted via novel compression methods. In other cases, manufacturing approaches such as the addition of moisture barriers can solve compatibility issues that would otherwise be intractable. Careful exploration of the optimal production and packaging approaches for a selected formulation is therefore crucial to the success of many FDCs.

Recommended documentation to expedite regulatory review and approval

Careful advance planning and a solid understanding of the issues of greatest interest to regulatory authorities can expedite the progress of FDC drug products through the approval pathway.

Scientific input for marketing approval of FDCs typically includes thorough demonstration of the appropriateness of the drug combination as well as documented fasted and fed bioequivalence studies, complete with the bio-equivalence study design and statistical plan. Addressing these considerations in early research can result in shorter review turnaround and faster marketing approval. Key topics that are likely to be required for registration of any new FDC are described in Table 3.

Scientific input for marketing approval of FDCs typically includes thorough demonstration of the appropriateness of the drug combination as well as documented fasted and fed bioequivalence studies, complete with the bio-equivalence study design and statistical plan.

While precise requirements for data and justification will depend on the type of application and reference formulation, as well as the regulatory body from which approval will be sought, close attention to these considerations will minimize the risk of major rework or delays.

Conclusion

Fixed-dose combination drugs have become an important alternative to monotherapy in the treatment of many diseases and conditions, including hypertension, diabetes, cancer, tuberculosis, asthma and COPD, and they hold promise for many more. Delivering more safe and effective products to patients requires understanding and overcoming multiple scientific and regulatory hurdles.

Technology-based solutions to identify compatible and potentially synergistic drug combinations can improve therapeutic options for patients and expand business opportunities for sponsors. By leveraging the information from these emerging drug databases, companies can build a more robust lifecycle for their existing products and identify opportunities in new indications.

Once initial selection is complete, a solid understanding of the key factors at play in formulation and manufacturing decision-making can help streamline the process for clinical research and market approval.

To learn more about the promise and possibilities of fixed dose combination drug development, contact us.

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Dr. Kane has more than 25 years of experience in the science and business of taking molecules through the entire drug development process. His extensive knowledge spans early stage development to scale-up and commercial manufacturing, and includes technical transfers between global sites and drug life cycle management. Dr. Kane received his Bachelors, Masters and Ph.D. degrees from the Bombay College of Pharmacy, University of Bombay, India, and served as a post-doctoral fellow at the School of Pharmacy, University of Cincinnati, Ohio. He has also earned an executive MBA from Richard Ivey School of Business, University of Western Ontario, Canada. Dr. Kane is a member of various international pharmaceutical professional organizations, and is often asked to speak about scientific topics on formulation, technology other technical aspects, QbD, etc at major industry events. He has also published many articles in International journals and delivered many talks at meetings and conferences cross the globe.

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