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What's Needed for Approval of Fixed-Dose Combination Products?

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Different Types of Combinatorial Approaches

A combination product is a therapeutic intervention for which more than one therapy or approach is used. This may include therapeutic and diagnostic products that combine drugs, devices, and/or biological products (e.g. device/drug or biologic/drug products) according to the U.S. Food and Drug Administration (http://www.fda.gov/CombinationProducts/AboutCombinationProducts/default.htm). In the case of drug products *per se* (i.e., drug-drug combination), they may be composed of several drugs (i.e., small-molecule and/or peptide) marketed as several separate pills, each containing a particular drug (co-packaging), or as single pills that contain several drugs (i.e., fixed-dose combination products).

In other words, a fixed-dose combination product (FDC) is a drug-drug combination for which all active moieties (drugs) are assembled with a fixed ratio of doses into one single pill. In some therapeutic areas such as cancer, HIV, malaria, tuberculosis or asthma, they have been used for more than 50 years [1]. Many advantages have thus been associated with FDCs - increased efficacy and/or reduced incidence of adverse effects, lower costs of manufacturing, simpler logistics (distribution), and improved adherence and compliance. For the industry, they constitute generally low-cost and low-risk projects increasing revenues and extending market exclusivity once original patents have expired [2]. From a clinical point of view, FDCs aim either at eliciting additive or synergist effects for the same indication or at inducing new effects for another indication. Examples of products of that first category are numerous. For HIV, asthma, hypertension, cholesterol, several FDCs have become gold-standards and blockbusters therapies. Atripla® (efavirenz/emtricitabine/tenofovir disoproxil fumarate), Advair® (fluticasone/salmeterol), Janumet® (sitagliptine/metformin), Symbicort® (budesonide/formoterol), Combivir® (zidovudine/lamivudine), Hyzaar® (losartan/HCT), Truvada® (emtricitabine/tenofovir) and Vytorin® (ezetimibe/simvastatin) have reached combined sales beyond 15 Billion USD annually [3]. One of the newest FDCs to reach market, called Xultophy® (degludec/liraglutide) is believed, according to Novo Nordisk, to become the next gold-standard against type 2 diabetes [4].

Better Effects for Same Indication or New Effects for another Indication

As mentioned earlier, most FDCs exhibit increased additive or synergistic effects for the same indication(s) the constitutive drugs had been originally approved for (see examples cited above). However, a relatively new type of FDC is emerging - products that can induce brand new effects for the development of new market(s). The FDA considers some of them as new chemical entity (NCE) specifically if one of the active moieties had never been approved. New effects with old drugs may also be considered as NCE with only 3 years of extended market exclusivity. For instance, in spinal cord injury (SCI), a FDC called Spinalon™ (levodopa/carbidopa/buspirone normally used for Parkinson's disease and anxiety, respectively) was recently found to potently reactivate spinal locomotor neurons and, hence, temporary elicit corresponding episodes of basic walking in chronic paraplegic animals [5]. It has recently completed phase I/II trials (https://clinicaltrials.gov/ct2/show/NCT01484184). For sleeping disorders, new CNS-mediated actions were found to be induced by THN102 - a FDC comprising an old drug modafinil (in low doses) and a new molecular entity THN02 (currently in phase II clinical development) [6]. Buprenorphine, originally approved as an anesthetic agent (opioid agonist), was recently approved (2014) in combination with naloxone (opioid antagonist) as a novel FDC called Suboxone® against opioid dependence [7].

Manufacturing and Bioequivalence Data

Obviously, if a FDC seeks approval for increased effects or for new effects-corresponding clinical data needs to be provided to regulatory agencies. But beyond that, issues regarding formulation and manufacturing need to be addressed properly [8,9]. For instance, when bringing together different APIs, the latter must exhibit physical and chemical compatibility to ensure that the different components do not generate new impurities or lead to drug–drug interactions. If chemically incompatible APIs are found, it is imperative to develop a multi-layer approach such as with an intermediate placebo layer to avoid interactions. Otherwise, mainly bioequivalence data in healthy individuals (phase I with 20-30 subjects) are expected by authorities for NDA approval to demonstrate that the each API maintains its PK/PD profile. For FDCs that propose new effects (using only old drugs), standard clinical data (phase II-III trials) are required although the phase I study in health subjects is not generally required since compelling safety data normally exist for each API [9,10].

Conclusion

The development of new FDCs is increasingly popular. In neurology, where innovative products are lacking, this may become a novel opportunity for the industry to ease and accelerate the development of new products [11].

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