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Editorial

Can Drug Combinations Ease Approval of New Promising CNS Products?

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Snapshot of the Industry

The worldwide crisis in 2008 and the patent cliff problems have had a devastating impact on the industry. Pharmaceutical companies have announced 156,000 jobs lost in the United States in recent years [1]. Global sales of prescription drugs have drastically decreased [2] whereas so-called Big Pharma such as GSK, AstraZeneca and Novartis have decided to significant decrease or even cease research activities in neurosciences [3]. Indeed, in these conditions, developing new psychotherapeutic drugs has become more than ever high-risk projects with low approval rates [3,4]. Unfortunately, many CNS diseases remain associated with significant unmet medical needs. In Europe, 38% of the population is diagnosed with a CNS disorder [5] whereas the global market for CNS therapeutics is expected to reach $129B US dollars by 2020, driven largely by the rapidly increasing market that is aging [6].

How to Increase Approval Rates

One of the avenues successfully explored in cancer, HIV, asthma or diabetes research has been the development of new drug combination products. In fact, many of them such as Atripla Advair or Janumet have become blockbusters therapies. Fixed-dose combinations (FDCs) – i.e., products including generally two or three active pharmaceutical ingredients (APIs) combined in a single dosage form with fixed doses, are of particular interest since generally associated with relatively faster approval especially if only 'old' off-patent molecules are used as constitute APIs [7]. Although, in CNS research, it has taken longer to be recognized as an interesting avenue to ease and accelerate approval of new therapies, FDCs count, as of 2013, for 22% of the CNS pipeline in development according to a report published recently by Drug Development [8]. For products composed only of known molecular entities or off-patent molecules, FDCs constitute undoubtedly low-cost and low-risk projects with promising therapeutic value as recognized recently by FDA who extended the periods of market exclusively after approval [9, 10].

Compelling Safety Data and Enhanced or New Effects are Key

There are several reasons for further developing new FDCs. Unlike simple drug combinations, FDCs comprise all APIs into one single tablet as mentioned earlier. For increasing patient compliance, it is definitely considered as a significant advantage. It is easier to remember taking one pill rather than two pills whereas fewer pills also mean faster self-administration. Finally, it is generally considered as safer since little to no chance for patients to mismatch doses of each API. But the greatest benefit associated with FDC safety is probably that

APIs with well-known safety profiles will end up increasing probabilities of successfully approved products, specifically if no drug-drug interaction is found with preclinical studies. Another key advantage of most FDCs beyond, faster development and lower costs, is efficacy. There is little question that many patients benefit from receiving more than one drugs to treat a disease when their actions are additive or even synergistic. For instance, Combivir (zidovudine + lamivudine) has been a gold-standard therapy against HIV some years ago, Advair (fluticasone + salmeterol) and Symbicort (budesonide + formoterol) against asthma generateted combined sales of 9.5B US dollars in 2009 or Hyzaar (losartan + HCT) against hypertension, Truvada (emtricitabine/tenofovir) against HIV, and Vytorin (ezetimibe + simvastatin) against cholesterol reached combined sales of 6.2B US dollars recently [11]. Novo Nordisk announced 18 months ago that Xultophy (degludec + liraglutide) is about to become the next gold-standard against type 2 diabetes (http://www.prnewswire.com). Moreover, there is compelling evidence that entirely new effects may also be found with some innovative FDCs. Indeed, partially acting upon two or three different families of receptor targets may uncover unsuspected beneficial effects. For instance, some evidence has been found in our laboratory after extensive drug screening studies showing that no single molecule, used separately as a monotherapy, could potently restore locomotor activity in animal models of paraplegia. In clear contrast, we discovered subsequently that a tritherapy called Spinalon (levodopa + carbidopa + buspirone) could potently reactivate spinal locomotor neuron and, hence, temporary induce corresponding episodes of basic walking in chronic paraplegic animals [12,13]. In France, Dr. Mouthon and Charveriat from Theraxus identified new CNS-mediated effects on sleeping disorders induced specifically by a combination of modafinil and THN02 (currently in phase II clinical development)[14]. In non-CNS areas such as cardio-metabolic disorders, Novartis recently obtained approval in the U.S. for a FDC called Entresto (sacubitril + valsartan) with first-in-class new effects on chronic heart failure through actions upon angiotensin and neprilysin receptors [15].

Concluding Remarks

Using known and safe molecules for the design of new FDCs is likely to ease and accelerate the development and approval of innovative CNS products that may also become gold-standards or first-in-class therapies capable of meeting the medical needs of neurologically impaired patients. It is worth mentioning that beyond that extended market exclusively recently announced in the US, FDC products can benefit from the 20-year period of patent protection provided that the patentability criteria are met - novelty, inventive step and industrial application [16].

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