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A Novel Approach for Innovative Pharmaceutical, Nutraceutical and Biocosmeceutical Products: Different Types of Combination Products and Co-activation of Natural Synergistically Acting Target-Receptors (CanSATs)

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Author's contribution

Author PAG was designed, analyzed and interpreted and prepared the manuscript.

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ABSTRACT

Traditionally, the main model of the pharmaceutical industry for developing new drugs has been based on monotherapies, new molecular entities (NMEs), and their underlying one-target-one-disease dogma. It is no surprise that closely related fields such as the cosmeceutical and nutraceutical areas, largely inspired by Big Pharma, have also mainly used that model. However, compelling evidence suggests that the time has come for these sectors of R&D activities to further explore more efficient, cost-effective and reliable approaches for innovative products. Among a few approaches proposed in recent years, there is one that is of particular interest – the 'combination drug' often referred to as the fixed-dose combination (FDC) products approach. It has been generally defined as two or more active ingredients that are combined in a single dosage form for

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either new effects or superior synergistic-like efficacy with less adverse effects. Both the World Health Organization (WHO) and the U.S. Food and Drug Administration (FDA) have recognized the great potential of FDCs for the future of innovation in those sectors. In fact, the development of FDCs has recently received substantial support for commercialization of new products – that is between three and five years of additional protection and exclusivity. Next-generation FDCs have already been identified. Indeed, FDCs that may be referred to as 'variable-dose combinations' (VDCs) products and, more specifically, 'Co-Activation of Natural Synergistically-Acting Target-Receptors' (CanSATs) products when applied to natural products if synergistic-like actions are found among active ingredients. Although VDCs and CanSATs have emerged mainly from the nutraceutical and cosmeceutical sectors, these approaches may perhaps also promote the development of promising new pharmaceutical products.

Keywords: Patent cliff problems; monotherapy; fixed-dose combination; cosmeceutical; pharmaceutical; CanSATs.

1. INTRODUCTION

Several experts have recently pointed out that the golden age of the pharmaceutical industry is past. Some have even declared that significant changes are needed to support innovation in that area in the future. On average, the cost of developing a new drug (i.e., New Molecular Entities or NMEs), which had substantially increased in the last twenty years, has gone beyond $1.3 billion U.S. dollars in recent years (i.e., including the cost of failures). It takes more time than ever to develop a new therapeutic – that is between 10 and 15 years of development to bring a NME to market [1,2]. With those significant hurdles, it is less than one product out of five or ten thousands potential candidates that succeeds at reaching market [3]. Consequently, and despite expensive state-of-the-art devices for identifying leads and new candidates, pharmaceutical companies are still not producing drugs any faster than they were before, several decades ago [4]. In fact, less and lessNMEs are approved each year [5-7].

In recent years, as an attempt to boost innovation and to accelerate the approval of new products, the great potential of fixed-dose combination (FDC) products has been explored. Because of less stringent regulations, in closely-related sectors such as the nutraceutical and cosmeceutical areas, FDCs and its newest evolutionary versions -VDCs and CanSATs- have emerged as one of the best solutions for innovative products in the food and skin care industries.

2. FIXED-DOSE COMBINATION PRODUCTS (FDCs)

According to the U.S. Food and Drug Administration (FDA) and the Federal Food, Drug, and Cosmetic Act (FFDCA), NMEs are products that are composed of an active moiety that has never been approved by the FDA or marketed in the U.S. In clear contrast, products that are composed exclusively of known molecular entities (so-called 'old' drugs) are referred to as combination products (source: www.fda.gov). This said, some combination products mainly include one or several NMEs.

In the pharmaceutical industry, they are particularly referred to as FDCs – that is a final product comprising two or more active ingredients that are combined in a single dosage form (also known as 'polypill' or 'combo pill') for either new effects or superior synergistic-like efficacy with less adverse effects. The World Health Organization (WHO) stated that FDCs have advantages when there is an identifiable patient population for whom treatment with a particular combination of actives in a fixed ratio of doses has been shown to be safe and effective, and when all of the actives contribute to the overall therapeutic effect. In addition, there can be real clinical benefits in the form of increased efficacy and/or reduced incidence of adverse effects [8].

Since the 1990s, the number of FDCs approved by regulatory authorities has kept augmenting. One hundred and thirty one (131) FDC products have been approved thus far in the U.S. (Table 1) [9]. Among them, FDCs for cardiovascular, endocrinological, infectious, neurological and respiratory problems and disorders have been developed and successfully commercialized [9]. In fact, many have become gold-standards in their respective classes.

The FDA has recognized the great potential of FDCs for the future of innovation. Indeed, for

FDCs that comprise at least one NME (also referred to as New Chemical Entity), five years of exclusivity is allowed. In turn, for new FDCs that represents a new use of old drugs, FDA is able to grant three years of patent protection [10]. Pharmaceutical companies are turning toward FDCs not only to increase innovation but also to diffuse the impact of generic competition, revitalize established brands, fill gaps in product pipelines, and enhance patient compliance. Generally, combinations of old molecules carry lower risk and adverse effect issues although high financial reward remains because the resulting product comes with new patents that protect it from generic competition.

The superior efficacy of FDCs has been shown first in the fields of cancer and HIV. According to Jim Kling, science and medical writer for The Washington Post and Scientific American, drug combinations, laboriously worked out in clinical trials, are the key to most cancer treatments [11,12]. Most drugs, from monoclonal antibodies to small-molecule kinase inhibitors, are most effective in combinations [14].

On the other hand, the mechanisms of action are often more difficult to identify clearly with FDCs compared with monotherapies (e.g., NMEs). For instance, beyond the known target associated with each active ingredient considered separately (as monotherapies), synergistic actions involved at the cellular and intracellular levels remain more difficult to investigate when all molecules are co-administered as FDCs.

As an example, we discovered a few years ago unsuspected effects induced by a FDC called Spinalon for chronic spinal cord injury cases. A combination of levodopa, carbidopa and buspirone (better known for their effects against Parkinson's tremor and anxiety, respectively) was found to acutely elicit and restore temporarily stereotyped locomotor movements in spinal cord-transected animals [13]. It is currently under clinical development (Phase IIA trials) in spinal cord-injured patients [14] although the detailed mechanism of action at the intracellular level has not been established clearly yet. Indeed, despite clear evidence showing a specific role for dopaminergic and serotonergic targets (D_1 and 5-HT_{1A} receptors) presumably belonging to neurons of the spinal locomotor network (a.k.a. CPG), interactions between intracellular pathways known to modulate cellular activity upon serotonin and dopamine transmembrane receptor activation remain unclear [15,16].

Interestingly, known transmembrane cell targets but unclear intracellular synergistically-acting actions characterize also three (3) additional FDCs composed of different active molecules that were found in our laboratory to selectively restore micturition, defecation and ejaculation, other complex behaviors generally lost or impaired in spinal cord injured-patients [17-19]. In virtually all cases though, drug-drug combinations developed for therapeutic purposes have been fixed-dose products for simplicity and regulatory reasons. However, in nutraceutical and cosmeceutical areas, where less stringent regulations exist, next-generation combination products have arisen – products for which doses are not fixed and, as such, that may be referred to as variable-dose combinations (VDCs).

3. NON-FIXED-DOSE COMBINATION PRODUCTS (non-FDCs)

Strictly speaking, non-FDCs have been known for several years. Indeed, non-FDCs include also products for which several specific molecules have not been comprised within a single final product. For instance, they may be assembled in the same package or not. This may be associated to some extent with an older approach called pharmaceutical compounding or traditional compounding where, typically, only form, taste or texture is was changed to fit the unique need of a patient.

The main disadvantage of these other forms of drug combination products is that no patent protection can be sought and, hence, no exclusively of commercialization may be obtained. The first ever co-packaged combination product was Bristol-Myers's Pravigard PAC that was approved by the FDA in 2003.

4. A NOVEL HYBRID APPROACH: VARIABLE DOSE COMBINATION PRODUCTS (VDCs)

Beyond, these earlier types of non-FDCs, there is now a few examples of next-generation products that have been marketed recently. Products comprising several active ingredients for which doses are not necessarily fixed. For some of the active ingredients, doses may indeed vary separately and accordingly with the specific segment of the market addressed for each declination of a particular line of products.

Table 1. Examples of fixed- and non-fixed combination products

Type	Name	Composition	Approval/ Registered year	Indication
FDC	Corzide	Nadolol+bendroflumethiazide	1983	Diuretic
FDC	Dyazide	Triamterene+hydroclorothiazide	1997	Diuretic
FDC	Combivir	AZT+3TC	1997	HIV
FDC	Glucovance	Glyburide+metformin	2000	Diabetes
FDC	Trizivir	Abacavir+zidovudine+lamivudine	2000	HIV
FDC	Kaletra	Lopinavir+ritonavir	2000	HIV
FDC	Advicor	Niacin+lovastatin	2001	Dyslipidemia
FDC	Benicar	Olmesartan+medoxomil/HCTZ	2002	Diuretic
FDC	Caduet	Amlopdipine+atorvastatin	2004	Hypertension
FDC	Advair	Fluticasone+salmeterol	2006	Asthma
FDC	PrandiMet	Repaglinide+metformin	2008	Diabetes
FDC	Simcor	Niacin-simvastatin	2008	Dyslipidemia
FDC	Exforge	Amlodipine+valsartan+hydrochlorothiazide	2009	Hypertension
FDC	Tekamlo	Aliskiren+amlodipine	2010	Hypertension
FDC	Tribenzor	Olmesartan+amlodipine+hydrochlorothiazide	2010	Hypertension
FDC	Juvisync	Sitagliptin+simvastatin	2011	Diabetes
FDC	Namzaric	Memantine+donepezil	2014	Alzheimer
FDC	Prezcobix	Darunavir+cobicistat	2015	HIV
FDC	Spinalon	Buspirone+levodopa+carbidopa	In Dev.	Spinal cord injury
NFDC	Pravigard PAC	copacked Pravastatin+aspirin	2003	Cardiovascular
NFDC	PrevacidNapraPAC	copacked Naproxen+lansoprazole	2004	Arthritis
NFDC	No name	copacked AZT+3TC+efavirenz	2006	HIV
NFDC	VictrelisPegatron	copacked Boceprevir+peginterferon+ribavirin	2012	Hepatitis
NFDC	ViekiraPak	copacked Ombitasvir+paritaprevir+ritonavir+dasabuvir	2014	Hepatitis
NFDC variable dose	Centrum Regular	Multivitamins	2009	General health
NFDC variable dose	Centrum Women	Multivitamins	n/a	General health
NFDC variable dose	Centrum Men	Multivitamins	n/a	General health
NFDC variable dose	Centrum Junior	Multivitamins	2009	General health
NFDC variable dose	Centrum 50+ W	Multivitamins	n/a	General health
NFDC variable dose	Centrum 50+ M	Multivitamins	n/a	General health
NFDC variable dose	Centrum Prenatal	Multivitamins	n/a	General health
NFDC variable dose	NeuroDrink Sleep	L-theanine, magnesium, 5-HTP	n/a	Energy enhancer

Type	Name	Composition	Approval/ Registered year	Indication
NFDC variable dose	NeuroDrink Sonic	L-theanine+vitaminB+alphaGPC+more	n/a	Energy enhancer
NFDC variable dose	NeuroDrink Bliss	L-theanine+vitaminB+alphaGPC+more	n/a	Energy enhancer
NFDC variable dose	IDC integral serum	Regen-16	n/a	Anti-aging
NFDC variable dose	IDC ultim-age W	Regen-16	n/a	Anti-aging
NFDC variable dose	IDC regen boost W	Regen-16	n/a	Anti-aging
NFDC variable dose	IDC eyes W	Regen-16	n/a	Anti-aging
NFDC variable dose	IDC neck W	Regen-16	n/a	Anti-aging
NFDC variable dose	IDC wrinkles M	Regen-16	n/a	Anti-aging
NFDC variable dose CanSATs	Vitabiotics Omega M	Omega-3-6-9-containing oils	n/a	General health
NFDC variable dose CanSATs	Vitabiotics Omega W	Omega-3-6-9-containing oils	n/a	General health
NFDC variable dose CanSATs	Vitabiotics Omega pregnacare	Omega-containing oils	n/a	General health
NFDC variable dose CanSATs	Sqin Body	Shea+tea+glycerin+urea+HA+more	2015	Dry skin/xerosis
NFDC variable dose CanSATs	Sqin Foot	Shea+tea+glycerin+urea+HA+more	2015	Dry skin/xerosis
NFDC variable dose CanSATs	Sqin face	Shea+tea+glycerin+urea+HA+more	n/a	Dry skin/xerosis

Probably the best examples of what may be considered as VDCs (terminology introduced for the first time in this article) are multivitamins. Just a few years ago, the vitamin industry was essentially composed of FDCs given that for each brand (e.g., Swiss Naturals® or Centrum®), the recipe was unique and has remained still. More recently, those companies have begun fragmenting their markets in the hope of increasing overall market size and sales. That is how a variety of different Centrum® became commercially available. Centrum® specifically adapted for men or women as well as Centrum® for young active or older people (50+, menopausal women, etc.) became available as over-the-counter products. Essentially, the same ingredients composed every one of these specialty products but doses may slightly vary from one to another. To stimulate innovation for increased sales, those companies went from single-market to market specialization.

A Quebec-based company, Integral Dermo Correction (IDC), has also launched a series of anti-aging products that share a common technological platform called Regen-16® based on a useful combination of sixteen active ingredients aimed at further slowing down different naturally interacting mechanisms of skin physiology associated with aging (source: IDCdermo.com).

The company Neuro Drinks has also tapped into VDCs by offering a variety of drinks essentially composed of the same ingredients but in different doses with specific claims about sleep, energy, or relaxation (www.drinkneuro.com).

5. A SUBCLASS OF VDCs: CO-ACTIVATION OF NATURAL SYNERGISTICALLY-ACTING TARGET-RECEPTORS (CanSATs)

The cosmetic industry has also entered drastic changes and transformations in recent years. Traditionally, cosmetics have been composed of excipients and non-active ingredients (in the pharmaceutical sense). For instance, for years, moisturizers have been composed of petrolatum jelly as main ingredient (e.g., Vaseline®, Cetaphil®).

As an alternative to surgical interventions aimed to fight the many signs of aging (breast enhancement, fat tissue removal, face lift, etc.), the cosmeceutical industry was born. Cosmeceutical products emerged as cosmetics that comprise also biologically active ingredients for medical or drug-like benefits. A plethora of expensive anti-aging creams, lotions and serums came up but most often with the classical one-target-one-disease approach – that is one featured active ingredient among the excipients composing essentially a moisturizing product.

From there, other companies have taken advantage of the main FDC principles – that is co-activation of several targets generally provides more efficacy than activation of just one type of target. For instance, LaBelle Cosmeceuticals based in California has developed dermatological products against premature aging by wisely combining forty different classes of active ingredients that are mainly botanical extracts (source: lbcosmec.com).

The omega supplements market has also been fragmented recently. Vitabiotics, a Norway-based company, has used basically the same recipe of mixed omegas but at different doses for junior, for pregnant women, for women in general or for men. In Canada, Adrien Gagnon has also developed a line of products containing omegas for kids to help brain development, for pregnant women to help brain, eye and nerve development or for elderly to promote general health and cardiovascular function.

Our team (under licensing agreement with a Canadian company) has also developed a VDC adapted to natural product-type of active ingredients, consequently referred to as – Co-Activation of Natural Synergistically-Acting Target-receptors (CanSATs). It essentially combines appropriate doses of a wide variety of complex natural products (e.g., shea butter, Labrador tea, canola oil, glycerin, black tea, hyaluronic acid, urea) containing different sets of natural active ingredients (vitamins, minerals, etc.). This approach has been tested clinically to demonstrate superior efficacy compared with positive comparators (e.g., one of the best moisturizer on the market composed essentially of petrolatum jelly and glycerin, https://clinicaltrials.gov/ct2/show/NCT02429206). It is aimed to be declined in several specific specialty products for body and foot ultra-moisturizing creams and serums (line of products called SQIN^{TM}) designed specifically for chronic dry skin (xerosis) in elderly or patients suffering of mobility problems and/or paralysis.

6. CONCLUSION

The golden era of the pharmaceutical industry is behind us. NMEs and monotherapies are no longer the best approach given the skyrocketed costs and average time required for a new therapeutic molecule to market. One of the most promising approaches to stimulate again innovation and to bring new products to market is the combination product approach. In just a few years, more than a hundred FDCs, VDCs or so-called CanSATs (for natural product combinations) have reached market for cancer, HIV, malaria, tuberculosis, multiple sclerosis, spinal cord injury and for foods (functional foods) and dermatological products (anti-aging, repairing and moisturizing). This may suggest that the future of innovative products in the global health industry is progressively getting brighter again although regulatory changes will have to be made for comparable innovations in the pharmaceutical industry.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

The author has declared that no competing interests exist.

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