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Lessons from Innovation in Drug-Device Combination Products

Daniela S. Couto^{a,b,c,*}, Luis Perez-Breva^{a,d}, Pedro Saraiva^e, Charles L. Cooney^a

Abstract

Drug-device combination products introduced a new dynamic on medical product development, regulatory approval, and corporate interaction that provide valuable lessons for the development of new generations of combination products. This paper examines the case studies of drug-eluting stents and transdermal patches to facilitate a detailed understanding of the challenges and opportunities introduced by combination products when compared to previous generations of traditional medical or drug delivery devices. Our analysis indicates that the largest barrier to introduce a new kind of combination products is the determination of the regulatory center that is to oversee its approval. The first product of a new class of combination products offers a learning opportunity for the regulator and the sponsor. Once that first product is approved, the leading regulatory center is determined, and the uncertainty about the entire class of combination products is drastically reduced. The sponsor pioneering a new class of combination products assumes a central

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role in reducing this uncertainty by advising the decision on the primary function of the combination product. Our analysis also suggests that this decision influences the nature (pharmaceutical, biotechnology, or medical devices) of the companies that will lead the introduction of these products into the market, and guide the structure of corporate interaction thereon.

Keywords: controlled drug delivery; transdermal patches; drug-eluting stents, primary mode of action

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1. Introduction

Combination products of drugs and devices have been in the market for more than half-century¹. Early examples of combination products seem to have required little interaction between the pharmaceutical and medical device industries. However, the increasingly sophisticated combination products brought to market over the last couple of decades [1] have furthered the need to develop drugs and devices collaboratively using resources from both industries. Classifying the resulting high-value combination products as either enabled drugs or enabled devices has become a challenge. Over the last decade, regulatory agencies have developed specific competences and regulations that address the increasing integration of drugs and devices observed in the latest generation of combination products. For example, the Food and Drug Administration (FDA) established the Office of Combination Products on December 24, 2002, according to the Congress enactment. The Medical Device User Fee and Modernization Act enacted by the Congress on October 26, 2002 [2], required the FDA to establish an office “to ensure the prompt assignment of combination products to agency centers, the timely and effective premarket review of such products, and consistent and appropriate postmarket regulation of” combination products. The Office of Combination Products is committed to support industry and FDA staff in “understanding this complex regulatory area” [3].

High-value combination products range from drug-eluting stents to transdermal patches. Despite their high market potential, high-value combination products present new technological and organizational challenges: they require new product development

¹ The metered-dose inhaler, developed in 1955 by the Riker Laboratories, is one of the earliest examples of combination products.

strategies and a new regulatory approach compared to traditional combination products, drugs, and devices. Traditional combination products were driven by the need to bring more convenient products to the final user and include prefilled insulin pens and condoms with spermicidal activity. The lack of a competitive advantage emerging from the combination itself precipitated the rapid progression of these products into widely available undifferentiated commodity products. By comparison, high-value combination products extract their competitive advantage from the technological sophistication of the combination and aim at enhancing the function of the medical device or drug. New regulations have contributed to clarify the approval process of high-value combination products, but have also made it challenging to determine at a glance when a product will be considered a combination product. Combination products combine two or three single-regulated entities: drug, biological and/or medical device. They can be physically, chemically, or otherwise combined or mixed and produced as a single entity. They can also be packaged together or separately as long as their use comprises the interaction or usage of both. This definition may sometimes lead to certain products being considered as combination products against the practitioner intuition (e.g. transdermal patches). In the United States (U.S.), the Code of Federal Regulations 21 CFR 3.2(e) defines what should be considered as a combination product in more detail.

In this paper we analyze transdermal patches and drug-eluting stents; both combine a device and a drug, but differ in their primary function. The transdermal patch is considered a drug with an improved delivery system, while the drug-eluting stent is a device functionally enhanced by a drug. In the case of drug-eluting stents, the drug and the device had been independently approved for individual administration prior to the approval of the drug-eluting stent as a combination product. In the case of transdermal patches, the drug is

often approved separately for patient administration, but the patch itself needs not to be approved as a device. The patch is perceived as a platform for drug delivery and it is arguable whether transdermal patches should be considered combination products. However, according to the FDA these examples are regulated as combination products and subject to different regulatory paths [2].

The regulatory agency designates the primary function of a combination product by its primary mode of action. In the FDA, the Office of Combination Products receives the combination product, determines its primary mode of action, and based on that assessment, re-directs it to the most adequate FDA center to proceed with the regulatory evaluation [2]. For example, the primary mode of action of a drug-eluting stent is device. Consequently, regulatory evaluation of drug-eluting stents is conducted by the Center for Devices and Radiological Health.

There are salient differences between how regulators assess primary mode of action and how it may be done pharmacologically. The latter is the mechanism by which a pharmacologically active substance binds to a molecular target affecting the biological or biochemical pathway inside a living organism. The former – and the one we will use throughout this paper – is a regulatory assessment of the primary function of the combination product.

The paper is organized as follows, after a brief overview of the sources of data and the methodology we followed, we examine the spectrum of combination products with an overview of drug-eluting stents and transdermal patches. We dive into those two examples further to analyze the evolution from the original device/drug into a combination product: from stents into drug-eluting stents; and the emergence of drug delivery systems in the context of transdermal patches. These two examples anchor our discussion about devices

whose function is enhanced with drug delivery and drugs that are delivered more effectively through a device platform. This seemingly fine distinction translates into completely different regulatory pathways and is at the core of the strategies available to companies introducing first-of-a-kind combination products to reduce development uncertainty. We discuss further these strategies as we identify the dynamics of innovation that drug-device products follow during product development in comparison with traditional device or drug development. Along with this discussion we present highlights on the data that supports our analysis in side boxes that complement the more comprehensive tables available in supplemental materials.

This discussion leads us to one of the key contributions of this paper: that the assessment of the primary mode of action of a combination product – often perceived as a barrier and a major source of uncertainty – is in fact a consequence of the kind of company pioneering the development process. We summarize this finding with a model that explains the role of pioneers, regulators, and incumbents in the development of combination products. This model builds on prior work on architectural innovation to motivate how disruptive innovation such as combination products relates to technology integration and the exploration of adjacent markets. This is a critical insight because it helps understand combination products (even transdermal patches) as the result of a sequential evolution that can be reproduced in future generations of combination products.

The paper concludes with highlights on the potential application of our findings and the model we propose in the development of new generations of combination drug-device products, their regulatory outlook and the strategic considerations for technology and market partnerships. This is the second main contribution of this paper to the literature in this area. These highlights outline a roadmap for the development of combination products

that considers the evolution of combination products as a function of the regulatory, technological, and corporate evolution.

While this work draws mainly from examples from the U.S. market, our preliminary analysis of other markets suggests that our conclusions are more general and broadly applicable to other geographic markets, as well as to the next generations of combination products, such as products resulting from tissue engineering.

2. Methodology

We listed and analyzed all the drug-eluting stents and controlled drug delivery system currently approved by the FDA and that required New Drug Application submission. This resulted in 12 drug-eluting stents and over 70 controlled drug delivery systems with market approval in the U.S.. We collected data from four types of sources: interviews with experts in the field, databases, Orange Book, financial reports and papers, and company websites. Information of drug-eluting stent approvals was collected from the FDA website [4], and re-examined at the companies websites and financial reports. All the clinical data was retrieved from the clinicaltrials.gov database, when searching for each individual sponsor, and complemented with scientific publications. All the deals related with the sponsor company of each combination product were searched in the recap.com database and company websites.

The table in supplement A lists information on controlled drug delivery systems sorted by sponsor company, drug, new drug application (NDA) number, date of approval and indications, and description. The information from this list was retrieved from the Orange Book [5], and crosschecked and complemented with Drug@FDA database [6]. In the Orange Book, we searched for particular dosage forms (all extended release forms,

implants, intrauterine devices, and inserts) and routes of administration (implantation, intravitreal, intracranial, intramuscular, intrauterine, subcutaneous, and transdermal). For each controlled drug delivery system, we complemented the sponsor information with information of the company that developed the device platform, the manufacturer, and the company currently marketing the combination product. This information was retrieved from the drug label approved by the FDA, deals at the recap.com database, and companies' websites. The analysis of the interactions between different stakeholders is supported by the information on the different roles (sponsor, manufacturer, manufacturing, and marketing) assumed by companies in different stages of development, as obtained from the aforementioned databases.

3. Device Function Improved by Drugs

Within the past two decades, two different generations of stents were launched into the market. The second generation delivered improved results with more sophisticated technology that imposed additional manufacturing and regulatory approval challenges. Companies that bridged both generations developed the expertise to provide more sophisticated medical devices that integrate and deliver drugs.

In 1994 the FDA approved the first stent – a bare-metal stent. It is an expandable metallic device that is deployed inside a stenotic blood vessel to dilate the occlusion using a catheter and a driving system. Stenosis occurs due to the formation of an atheromatous plaque inside the blood vessel. The stent is applied to improve the blood flow by expanding the occlusion. Stents are simple solutions – less invasive and highly deliverable – when compared with previous standards of care, such as coronary bypass. Though stents were shown to be highly effective and reduce the rate of restenosis, when compared to balloon

angioplasty, in-stent restenosis is still a major complication after stent deployment [7,8]. Patients with stents may develop stenosis inside of the stent, leading to occlusion of the blood vessel again.

In 2003, less than one decade after the first stent was introduced in the U.S. market, the FDA approved the first drug-eluting stent. A drug-eluting stent combines a drug enclosed in a polymer that coats the metallic framework, the integration of drug and polymer determines the mechanism for controlled drug release [9]. Although technically more complex than bare-metal stents, drug-eluting stents have been found to outperform bare-metal stents [10]. The drug-eluting stent combines the mechanical action on the blood vessel blockage with the release of drugs that inhibit restenosis to decrease the problem of in-stent restenosis associated with bare-metal stents [11,12]. Since 2003, new drug-eluting stents were developed for patients with a broader range of complications associated with stenosis, such as multiple lesions, small vessels, long lesions [13], and diabetes [14,15]. The additional burdens associated with the integration of technologies, manufacturing, and regulatory approval of drug-eluting stents helped the companies that bridged bare-metal and drug-eluting stents retain competitive advantage through the development of key expertise advancing sophisticated medical devices that integrate and deliver drugs.

4. Drug Delivery Improved by Devices

Since the 1970s, the FDA has approved over 70 controlled drug delivery combination products (see Fig. 1 and Supplement A). By the 1980s ten controlled drug delivery products were approved spanning over three categories: transdermal patches, ocular implants, and intrauterine devices. During the 1990s as drug-delivery technologies became increasingly sophisticated controlled drug delivery products diversified further into: subcutaneous

implants, vaginal rings, buccal systems, and wafers (Fig. 1a). Technological sophistication enabled new approaches to drug delivery systems beyond transdermal patches to address highly specific needs; in particular, therapies that stood to benefit from more invasive drug-delivery solutions than transdermal drug delivery (see Fig. 1c and Table in Supplement A listing all controlled drug delivery products approved by FDA by indication). Gliadel® is an example of this technological evolution: Gliadel® is a wafer containing carmustine (7.7mg), a chemotherapeutic drug, homogeneously distributed in a biodegradable polyanhydride copolymer that is applied inside the brain as an adjunct to surgery for the treatment of glioma patients.

Fig. 1 shows the number of FDA approved controlled drug delivery systems by type of system and therapeutic indication. Transdermal patches account for over 60% of all controlled drug delivery systems available in the market (Fig. 1b). The technology of transdermal patches has been extensively described elsewhere [16-18], here we focus instead on the evolution of patches and controlled-drug delivery systems through technological generations.

Transdermal patches offer an alternative for controlled delivery of substances into the bloodstream through the skin, that is particularly suited for the delivery of potent drugs that may be poorly absorbed – or extensively metabolized – when administered orally. Their initial adoption can be explained by their ease-of-use, convenience, and increased patient compliance. The first generation of patches only allowed for passive diffusion of the drug through the skin, later generations introduced active methods of diffusion.

The first generation of transdermal patches was essentially limited by the passive methods of drug diffusion to deliver small, lipophilic, low-dose drugs [18]. Two different designs

competed in this first generation: reservoir-type (regulated by membrane and skin permeability) and matrix-type patches (regulated only by skin permeability) [16].

The second generation of transdermal patches introduced active methods of diffusion that enabled the delivery of larger molecules and improved control over diffusion rates [16].

This new generation uses chemical enhancers, noncavitational ultrasound, and iontophoresis to facilitate drug delivery [18]. Iontophoretic systems are an example of active transdermal patches, active diffusion is achieved with a residual electric current that helps widen skin pores and facilitates diffusion of larger molecules through the skin.

The third generation of patches introduced new active diffusion technologies that cross the skin's barrier layer of „stratum corneum”: microneedles, thermal ablation, microdermabrasion, electroporation, cavitational ultrasound, and synergistic combinations thereon [17-20]. The third generation is currently under clinical trials and is expected to revolutionize the delivery of large molecules and vaccines [21,22].

5. Dynamics of innovation in combination products

The development of a combination product involves a very specific pattern of interactions between several firms and regulatory agencies. Our longitudinal study of drug-eluting stents and transdermal patches suggests that the dynamics of innovation in combination products can be readily summarized by the roles assumed by pioneer, incumbent, and regulatory agency in the product development process and in the determination of the primary mode of action. We refer to established firms in the focal market that we are studying (medical devices or pharmaceutical) as *incumbents*. The focal market is the market that is either being disrupted by technological change (introduction of combination products), or adjacent to it. Pioneers are the sponsors introducing the first of a class of

combination product. Fig. 2 illustrates the roles of the pioneer, incumbent, and regulatory agency across product development.

During the development phase, the pioneer licenses complementary technologies and integrates them into a full combination product. Subsequent phases are determined by the primary mode of action that plays a pivotal role leading into the clinical study phase. Our research suggests that the actions assumed by each player before the determination of the primary mode of action have a strong bearing on the assessment of the primary mode of action. It is these actions that drive the dynamics of innovation in combination products; more specifically they drive the development of the technology and product, the reduction of regulatory uncertainty, and the structure of corporate partnerships.

From a technological vantage point, the pioneer acts as an integrator of complementary technologies that are generally licensed from third parties. The way in which the pioneer chooses to integrate these technologies into the product design shapes corporate partnerships and informs the primary mode of action assessment. Corporate interaction with technology partners is established through license agreements, and what is claimed in the description of the intended use submitted to the regulator advises the primary mode of action.

From a regulatory vantage point, the regulator's first task is to determine the center best suited to lead and support regulatory approval based on the input from the sponsor and the submission documents. That is the determination of the primary mode of action, which defines the regulatory approval pathway (medical device, drug, or biologic). This assessment has further consequences as it indirectly determines the profile of the incumbent that is more likely to advance product development and market launch.

From a corporate vantage point, as product development progresses, the incumbents that were identified after the primary mode of action assessment take-over gradually from the pioneer the role of shaping corporate partnerships. As the product approaches market, corporate interactions focus on market rather than technology and the incumbents are generally better positioned to select and decide how to market the combination product. This phase involves considerations about market, distribution channels, and service networks generally available to the incumbent as well as the financial support required to pursue regulatory approval and commercialize the combination product. Once the first of a class of combination products is marketed, it rapidly becomes a dominant standard (for a technology, a product, and a regulatory pathway) allowing other incumbents to become fast followers.

5.1. The pioneer sets the path

Our analysis suggests that pioneers that bring the first product of a class of combination products have an impact in the innovation dynamics of the entire class, not just in the specifics of the technological integration that led to the combination product. The pioneer touches on the three levers that result in the primary mode of action: integrates technologies into a new design, frames the regulatory assessment for this product and for the ones that will follow, and creates the structure of corporate partnerships through licensing of complementary technologies.

Pioneers are new entrants (firms or independent business units) that prove successful in disrupting the industry with the introduction of a new design of combination product.

Christensen defines disruptive technologies as the ones that bring a different value proposition to the market, resulting in typically cheaper, simpler, smaller, and more

convenient products and that ultimately precipitate the technology failure of the leading firm [23]. Our findings mirror Christensen's findings in other industry sectors [23]: business units of larger firms are likely to become pioneers when they retain a degree of independence and can define its own processes and business model. For this reason, when the pioneer is acquired Christensen and Kaufman [24] argue that to continue to promote innovation the parent company must preserve the independence of the acquisition instead of rushing to integrate it into an existing business unit.

Alza Corporation ("Alza") and Cordis Corporation ("Cordis Corp.") were two pioneers, with very specific business competences, that disrupted the industry in their respective area. Cordis Corp. released the first bare-metal and drug-eluting stents to the market. Alza led the way in developing controlled drug delivery systems, in particular the transdermal patches. These two examples are explored in more detail in Box 1.

5.2. Architectural innovation is at the basis of combination products

Combination products are examples of architectural innovation in the sense described by Henderson and Clark [29]. The pioneer, and later the incumbents, license complementary technologies and integrate them with its core technology to develop the combination product. According to Henderson and Clark architectural innovations keep the core concept unchanged and focus on the way in which components of a product are linked together [29]. This means that the basic knowledge underlying the core components is unaffected too.

Combination products are architectural innovations because they maintain a core concept and reinforce it with sophisticated linkages between the core technology and the complementary components are modified.

The notion of architectural innovation is critical to understand the impact the profile of the company (whether pharmaceutical, biotechnology, or medical devices companies) has at the technological level to discriminate core and complementary technologies. The way in which drug-eluting stents and controlled drug delivery systems emerges illustrates the notion of architectural innovation as it relates to the creation of a combination product. We overview this in further detail in Box 2. In the case of drug-eluting stents, the complementary technologies (drug and polymer) are licensed and integrated into the device platform by the device company. In the case of controlled drug delivery systems, the complementary technologies (platform to deliver drug) are licensed and integrated with the drug by the drug company.

Architectural innovation has strong implications on the development of complementary skills and the accretion of company infrastructure. In addition to integrating technologies, the firm needs new equipment, multidisciplinary know-how and skills, and development of new test methods. For instance, drug-eluting stents likely resulted from the work of multidisciplinary teams of engineers, biomaterials scientists, pharmaceutical scientists, and many different clinical specialists (as inferred by Burt and Hunter [30]). On the other hand, testing medical devices typically includes assessing physical and mechanical properties, while testing drugs or biologics focus on analytical and bio-analytical chemistry, and biological potency tests. The medical device companies that pioneered drug-device combination products lack typically the expertise to develop, integrate, and test drugs and likely acquired those new competencies typical from the pharmaceutical space while integrating drug and device.

5.3. Primary function decreases uncertainty

The primary mode of action plays a pivotal role bridging product development and the clinical study phase and in subsequent phases, it correlates with the structure of corporate interactions that emerges. Accordingly, the assessment of the primary mode of action is often perceived as the single biggest risk-mitigating milestone for combination products. However, despite the perceived prominence of the primary mode of action in the process, our analysis suggests that it is the actions assumed by each stakeholder, not the assessment itself, that drive the dynamics of innovation in combination products. In other words, to an external party, the primary mode of action represents a good descriptive indicator that clarifies strategy going forward. However, for the pioneer or any of the parties involved in the co-development of a new kind of combination product there are ample opportunities to predict the primary mode of action from the strategic choices done before the regulator does the actual assessment.

The determination of a primary mode of action narrows the scope of subsequent development and clinical milestones in ways that make the combination product more appealing to different kinds of incumbents. It will clarify the milestones ahead for an incumbent to advance product development and eventually market the combination product. If a combination product is considered as device, then a medical device company is better positioned – and more likely – to drive the regulatory approval. The Table in Supplement B illustrates this point with a sample list of combination products obtained from the webpage of the Office of Combination Products, sorted by the type of the primary mode of action (medical device, drug, or biological), and annotated with the clinical indication, approval date, and the company that developed it. The data suggests that the company sponsoring the product through the regulatory process is the company focused on

the core technology that is associated with the primary mode of action. That is, the sponsor is a medical device companies when the primary mode of action is a device, biotechnology or biopharmaceutical companies when it is a biologic, and pharmaceutical companies when it is a drug.

The determination of a primary mode of action for the first-of-a-kind combination product is critical because the regulatory framework for combination products is established by precedent: the primary mode of action of the first-of-a-kind sets the precedent for the entire class. Subsequent entrants may then perceive that this assessment decreases the uncertainty for the entire class.

In practice this means that the existence of an extra step for the „first-of-a-kind’ combination product increases the perceived risk of developing a combination product when compared to a traditional drug or medical device. However this risk is effectively mitigated by the fact that the way a pioneer describes the product, its claims, and its intended use to the regulator is largely influenced by its core technology. For example, an antibiotic-coated implant may be regulated as a device or as a drug according to the intended use and claims. If the intended use of the antibiotic is to prevent colonization on the implant, then it is likely regulated as a device. If the claim says the coating prevents infection, it might be classified as a drug. These descriptions are strongly linked to how the pioneer perceives the technology and its core competence. And not surprisingly, the assessment of the primary mode of action correlates with the kind of company that submits the combination product. The additional regulatory step adds a marginal degree of uncertainty for the first-of-a-kind combination product relative to drugs or medical devices, but that uncertainty is mitigated for subsequent entrants with products in the same class.

5.4. Incumbents decide to market

Our analysis suggests that incumbents leverage their stronger financial and market position to support product development of the first of a class of combination products, and advance subsequent cycles of product development for that same class.

As product development progresses and the primary mode of action is determined, incumbents take-over from pioneers the role of shaping corporate partnerships. They license the technology from the pioneer and reshape the earlier technology-based partnerships to accommodate their marketing efforts as they assume control over the last stages of product development. Our analysis shows that big medical device and pharmaceutical companies supported and introduced, respectively, drug-eluting stents and controlled drug delivery systems to the market. We explore in detail the role of incumbents in the development of drug-eluting stents and transdermal patches in Box 3.

Incumbents enter combination product development when all previous uncertainties have been mitigated and the only uncertainties that remain relate to traditional regulatory pathways, the market, distribution channels, and the service networks they have access to. These findings are supported by Schumpeter's later work, in which he stated that incumbents with capital and market power are in a stronger position to exploit innovation [32]. Different authors build on this theory. Teece identifies factors such as specialized manufacturing capability, access to distribution channels and service networks, and complementary technologies as the assets that confer incumbents with an advantage to exploit innovation [33].

Once the first-of-a-kind combination product is marketed, regulation „by precedent' allows it to become a dominant standard rapidly (at technological and regulatory levels). When the first-of-a-kind combination product obtains marketing approval, the pathway for approval

is defined and the marginal uncertainty disappears, allowing other incumbents to become fast followers.

6. Conclusions

Combination drug-device products are a disruptive technology category in modern drug delivery devices, representing a unique combination of performance, design, application and in some cases business partnering and technology licensing. This novel therapeutic product category has introduced new dynamics in medical product development, regulatory approval processes, and corporate interaction. Case studies of drug-eluting stents and transdermal patches facilitate a detailed understanding of the challenges and opportunities introduced by combination products when compared to previous generations of conventional medical or drug delivery devices. Drug-eluting stents and transdermal patches represent high-value combination products, in which drug and device have both a primary and an ancillary function. In both cases, combination products were developed to improve the function of precedent, clinically approved products.

The emergence of sophisticated combination products has brought the pharmaceutical and medical device industries closer; firms from each industry play now complementary roles in the development of drug-device products. Start-ups, new divisions of established companies, and incumbents from either industry interact to integrate and develop drug-device technologies and have leveraged expertise from each other in product development, testing, marketing, and distribution. The new drug-device products that find a competitive advantage in the combination itself and yield high value combination products created a new market space at the intersection of the pharmaceutical and medical devices industries.

The emergence of these high-value combination products has triggered new regulatory, strategic, and technological challenges that signal a divergence from traditional drug/device development. Future sponsors of new combination products may perceive this divergence as a source of risk, particularly regulatory risk. The regulatory cornerstone is the perception of the assessment of the primary mode of action as an additional step in the regulatory process that adds product development and regulatory risk much like the subsequent phases of drug development. Our analysis shows that the assessment of the primary mode of action adds marginal risk to the development process, rather, it is consequent with the value the original sponsor (the pioneer) perceives in the combination and helps incumbents rationalize and plan the resources they will need as they take over from pioneers the task to bring the product to market. Indeed the assessment on the primary mode of action is a good proxy to understand the evolution a product will undergo throughout its development and the co-evolution of partnerships that will be necessary to bring this product to market; and because the assessment itself has thus far been predictable for the majority of products in the market, we may derive a simple model that overviews the expected co-evolution of technology and strategy for future entrants in the combination products space.

The roles assumed by pioneer, incumbent, and regulatory agency in product development determine predictably the dynamics of combination products. The pioneer integrates complementary technologies into a new design, in so doing, it shapes the early technology-based partnerships and informs the primary mode of action assessment. The regulator takes into account the submission documents to assess the primary mode of action and forward the product to the right center that will lead the regulatory approval as if it were a drug, a device or a biologic. Incumbents assume control of product development at later stages, and the primary mode of action informs how they may leverage their resources and existing

partnerships as considerations about the market, distribution channels, and service networks become more prevalent. Once the first-of-a-kind combination product is marketed, it rapidly becomes a dominant standard, allowing other incumbents to become fast followers. These dynamics show how many new entrants approach the introduction of a combination product strategically. Firms, in particular start-ups or new divisions, may use the complementarity of drug-device technologies to capture new market opportunities: to expand within the combination product market, into the drug market, or the medical device market. Start-ups developing a new type of combination product that overcomes the limitations of a single-regulated product might be able to leverage the complementary resources of the incumbent to accelerate the development of the combination product and its marketing, while acquiring the expertise to go through the entire product development life-cycle for future generations of the combination product.

Expansion within the combination product space is, perhaps, the most promising area of development for new products. The regulatory advances in combination products, and the observation that the competitive advantage of current combination products lies in the sophistication of the combination would seem to indicate that this generation of combination products has established a new high-value market. The advent of new technologies combining drug, device, and biologics that are currently being researched suggests that this is a growing market. Newly emerging biomedical technologies including cell-based therapies, new biosimilars and fragile, expensive biologics, nanotechnologies, molecular diagnostics, and tissue engineering are expected to provide new opportunities in bridging device and drug capabilities and synergies, bringing increasingly sophisticated combination products to the forefront. The model here proposed can also be applied as tool

by start-ups and incumbents in understanding how to strategically capitalize on the developed of combination products.

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Box 1. The pioneers Cordis and Alza disrupted drug-eluting stents and controlled drug delivery systems

Cordis Corp. was founded in 1959, with the aim of establishing a strong business core in vascular disease management. In 1994 it launched the first stent to the market (PALMAZ-SCHATZ® Balloon-Expandable Stent). In April of 2003 the FDA approved the first drug-eluting stent developed by Cordis Corp., Cypher sirolimus-eluting coronary stent. Cordis Corp. was the pioneer in both generations of stents. It was a major player in interventional cardiology during the 1990s [24]. In 1996 Johnson & Johnson acquired it to form Cordis division. In this year, the interventional cardiology market was estimated at \$2 billion worldwide, with a 20-25% annual growth rate [25]. With the support of Johnson & Johnson resources, Cordis was the first company to bridge both generations, upgrading the stent platform into a drug-eluting product.

Alza was a pioneer and played a key role in the disruption of controlled drug delivery systems. Alejandro Zaffaroni founded the company in 1968. Since then, Alza developed the first ocular implant, the first intrauterine device, and the first transdermal patch. Based on

the D-Trans® platform, Alza developed the six first transdermal patches commercially available in the U.S. market: Transderm Scop®, Transderm-Nitro®, Catapres-TTS®, Estraderm®, Duragesic®, and Nicoderm®. The D-Trans® platform is a multilayer patch with the drug stored in a gel reservoir. Alza also had a major role in the disruption of active transdermal technologies. It developed the E-Trans® platform and IONSYS™ iontophoretic system, which was approved in 2006 by the FDA [7]. Alza sponsored the regulatory process under the support of the parent company, Johnson & Johnson, because, similarly to what happened with Cordis, Alza was acquired by Johnson & Johnson, in 2001, through a stock-for-stock transaction worth \$10.5 billion [26].

Box 2. Complementary technologies are licensed to integrate drug-eluting stents and transdermal patches

In the case of drug-eluting stents, medical device companies developed the medical device (in blue, Fig. 3 a.) and assembled it with the drug (in red) licensed from a pharmaceutical company and the polymer (in yellow) typically licensed from a small company. The polymer works as a matrix that covers all the metallic structure and encloses the drug for controlled release. Medical device companies acquired or licensed the required assets to evolve from the first to the second generation of stents. They extended their expertise in the market, developing more sophisticated products. From the four different drugs used in drug-eluting stents currently available on the market, three were already commercially available as pharmaceuticals for other applications. The intellectual property licensees of the drugs are Wyeth (sirolimus), Novartis & AG (everolimus), Angiotech (paclitaxel), and Abbott Laboratories (zotarolimus).

In the case of transdermal patches, the companies that develop and/or manufacture the controlled drug delivery systems are not involved in marketing and distribution of pharmaceutical products. Usually there is a symbiotic interest from the pharmaceutical company in delivering the drug (red, in Fig. 3b.) through a transdermal system (blue) developed by a specialized company. The usual ways of cooperation are: (1) the patch platform is licensed to a pharmaceutical company and the company retains the rights of manufacturing or charges for the manufacturing by third parties; (2) joint development with pharmaceutical industry; (3) the company develops the transdermal patch and partners with a large pharmaceutical company for the utilization of their sales force and marketing expertise. Companies developing transdermal patches are typically small companies that build their core business in drug delivery systems. They don't have the resources to pursue clinical development by themselves and/or developing marketing and sales forces. As these companies are successful and expand in time, they seem to evolve from the first/second to the second/third forms of cooperation mentioned. Alza illustrates an example of this progress. Alza had commercialization and joint development agreements with Novartis, Boehringer Ingelheim, Janssen Pharmaceutica, and Sanofi-Aventis. After 1993, Alza developed, manufactured, and marketed Testoderm® and Testoderm® TTS. Alza shifted from being strictly a licensor to a fully integrated company, and its revenues increased from about \$40 million in 1992 [27], to \$131.2 million in 1996 [25].

Box 3. The role of incumbents in the development of drug-eluting stents and transdermal patches

Big medical device companies were the key actors in making the transition between bare-metal drug-eluting stents. Besides Cordis (and Johnson & Johnson), Boston Scientific

Corporation, Medtronic Vascular (from Medtronic), and Abbott Vascular (from Abbott Laboratories) played a decisive role in disrupting drug-eluting stents. These four companies created a devoted division or subsidiary unit to the interventional cardiology area. The devoted division or subsidiary unit confers a certain independence and freedom to operate and develop a product that is not directly aligned with the company pipeline.

After the approval of Cordis' Cypher® by the FDA in 2003, 11 other drug-eluting stents were released to the U.S. market, though there are only six different platforms currently in the market. This is illustrated in the Fig. 4. Boston Scientific has itself three platforms and eight different products in the market. Five of them are incremental improvements over the Taxus® platform. Promus® is a platform developed by Abbott's Xience V® Everolimus. This resulted from a previous agreement, when Boston Scientific acquired Guidant Corporation.

Big pharmaceutical companies played an important role in the disruption of transdermal drug delivery systems. Indeed, 62% of the overall transdermal patches were or are marketed by big pharmaceutical companies. This is illustrated in Fig. 5. For example, Novartis launched eight different transdermal patches into the market, which resulted from collaborations with Alza, Noven, and Lohmann Therapie-Systems AG. Novartis also founded Novogyne, a joint venture with Noven, with the purpose of developing transdermal patches. Johnson & Johnson launched five different transdermal patches, including Duragesic® and IONSYS®, developed by Alza. Bayer markets three different transdermal patches, developed jointly with 3M Pharmaceuticals. Watson Laboratories marketed three different transdermal patches: two developed in collaboration with TheraTech and one developed in-house. Alza also launched two transdermal patches on its own, Testoderm® and Testoderm TTS®. The other 24 transdermal patches were individually released from

different entities. Big pharmaceutical companies, such as Boehringer Ingelheim, Sanofi-Aventis, Astrazeneca, Pfizer, Bristol-Myers Squibb, and Merck & Co released a single transdermal patch to the market. There are two key considerations that might help understand why big pharmaceutical companies have only one transdermal patch. First, big pharmaceutical companies often seek partnerships to developed transdermal patches when the product can be marketed successfully within their existing portfolio. Second, the drug has to comply with the technical requirements to be part of a transdermal patch. When the two factors are aligned, big pharmaceuticals typically invest in the development of a transdermal patch. Also, drugs facing patent expiration can get a new life if the drug is combined with a device as a combination product. This solution may provide some short-term relief to the pharmaceutical industry [30].

Fig. 1. Controlled drug delivery systems approved by the FDA: (a) Cumulative number of controlled drug delivery systems approved per year per type of delivery system (the legend is the same as for b); (b) Number of delivery systems per type approved by the FDA; (c) Number of delivery systems approved by the FDA by therapeutic indication. These numbers include market-discontinued products, but not generic forms of delivery systems. The number of discontinued products corresponds to approximately 38%.

Fig. 2. Representation of the lessons learned in the dynamics of innovation of drug-device combination products from the corporate, technological, and regulatory vantage points. A pioneer sets the path by introducing a new technology into the combination product space. Complementary technologies are licensed to integrate it into a full combination product. The FDA determines the primary mode of action of the combination product, which is a

crucial step that influences the company profile – medical device, pharmaceutical, or biopharmaceutical – that takes the product through regulatory approval into the market.

Fig. 3. Schematic representation of the assembly of combination products: a. Drug-eluting stents are built-up on a device platform (in blue), and a drug (in red) together with a polymeric coating (in yellow) integrated into the device platform; b. A drug (in red) is integrated into a device system (in blue). Black pins represent the primary mode of action of the combination product.

Fig. 4. Timeline showing drug-eluting stents date of approval by the FDA. Cordis' Cypher® was the first drug-eluting stent to be approved, in 2003. The second drug-eluting stent that was approved by FDA was Taxus® Express2® Paclitaxel-Eluting from Boston Scientific Corporation, in 2004. The following three drug-eluting stents were approved in 2008. Medtronic Vascular's Endeavor® Zotarolimus eluting was approved in February. Xience V® Everolimus from Abbott Vascular was approved by the FDA in July. Xience V® is also being marketed by Boston Scientific under the name of Promus®. Taxus® Express® Atom™ and Taxus® Liberté® were approved by the FDA in 2008. Taxus® Liberté® Atom™ and Taxus® Liberté® Long™ were approved in 2009. ION™ Paclitaxel-Eluting is a new platform developed by Boston Scientific and approved in April 2011. Xience Nano® Everolimus from Abbott Vascular was approved by the FDA in May 2011, which is also being marketed by Boston Scientific under the name of Promus® 2.25.

Fig. 5. Timeline showing transdermal patches date of approval by the FDA. Novartis launched eight different transdermal patches to the market during the last three decades, while Johnson & Johnson, Bayer, and Watson Labs launched 12 in aggregate during the last two decades.

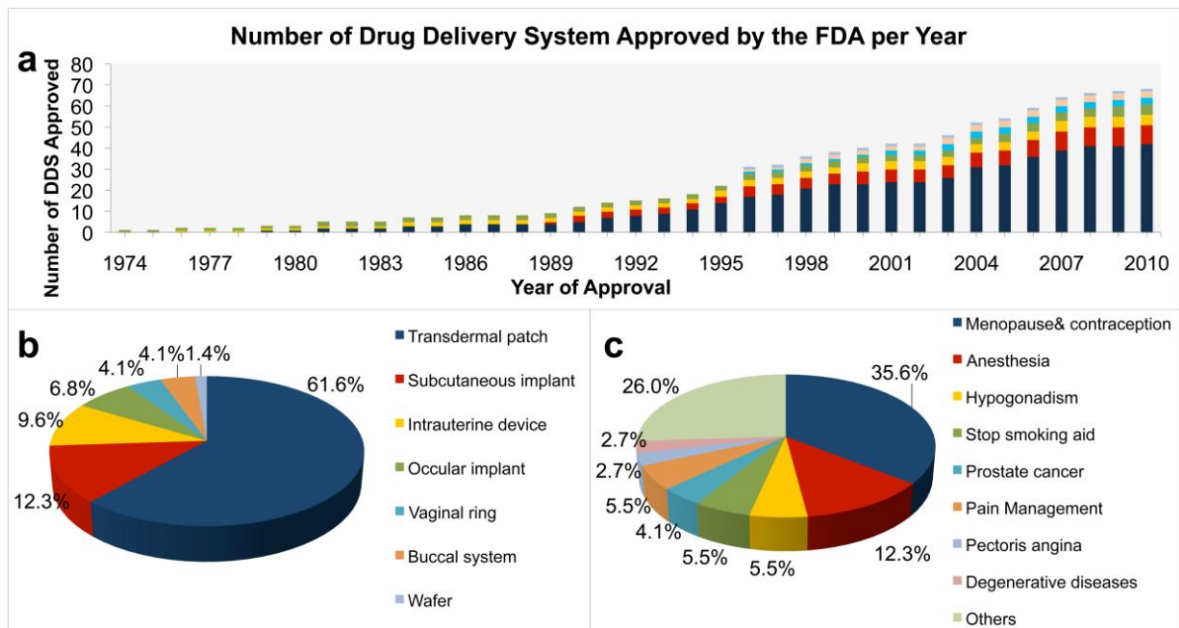


Figure 1

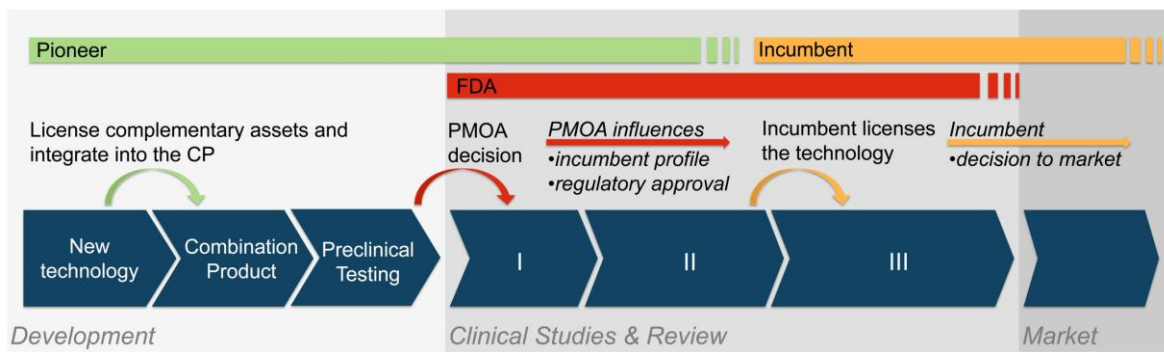


Figure 2

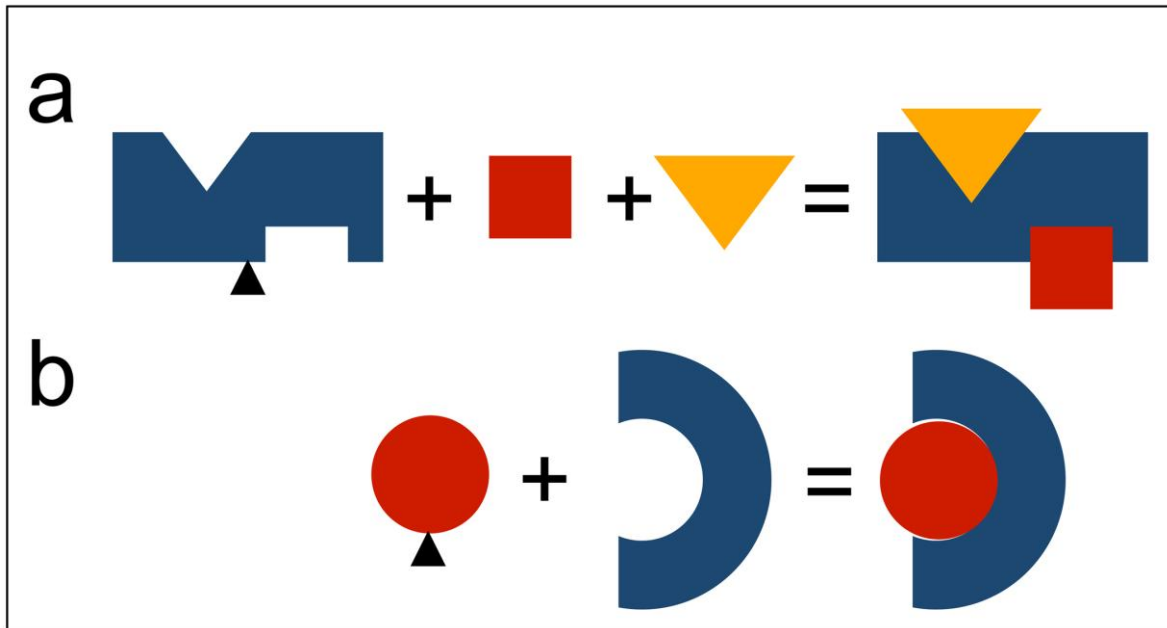


Figure 3

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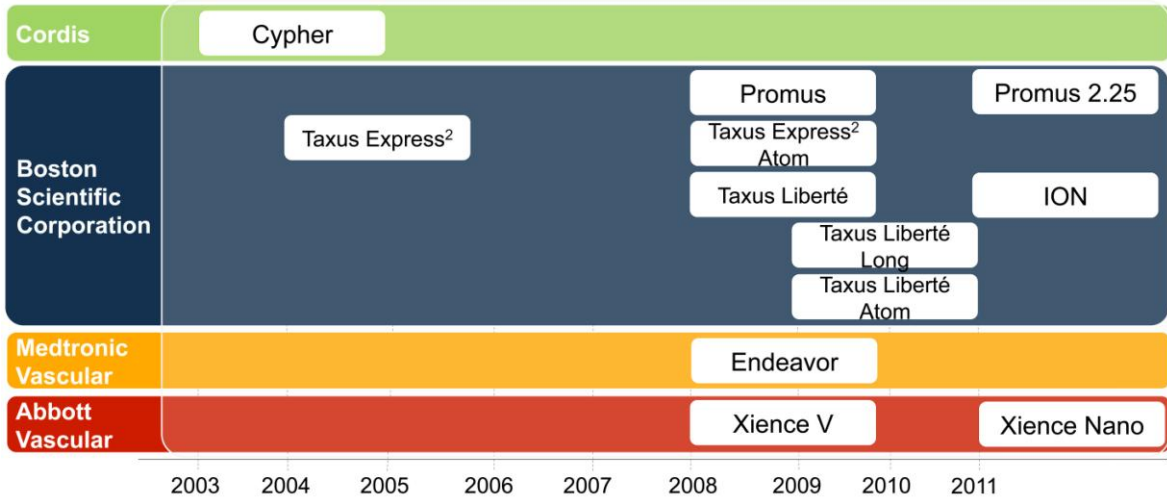


Figure 4

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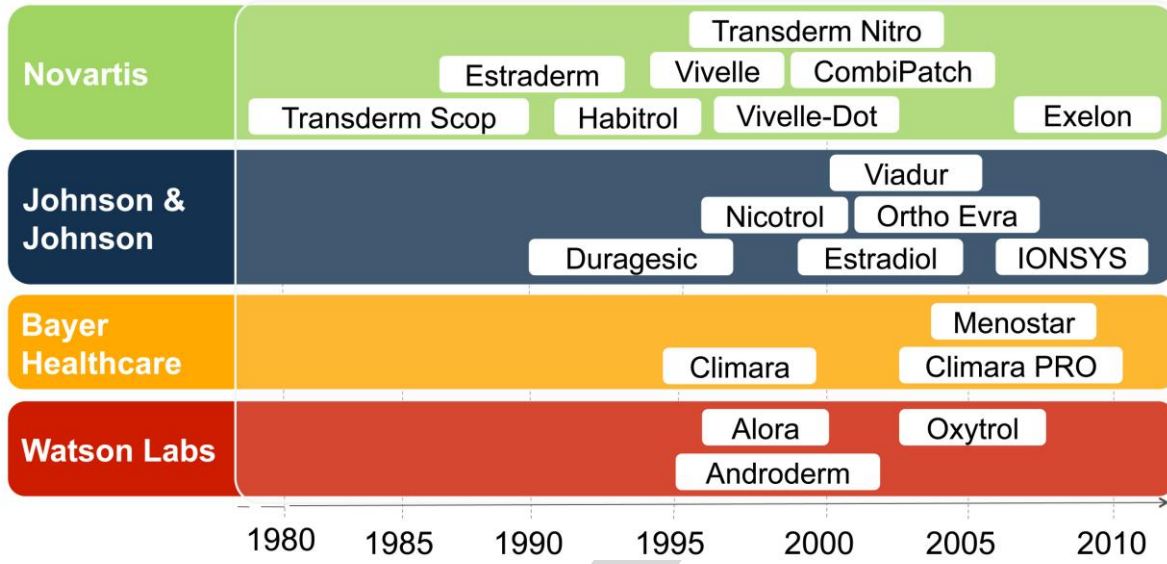
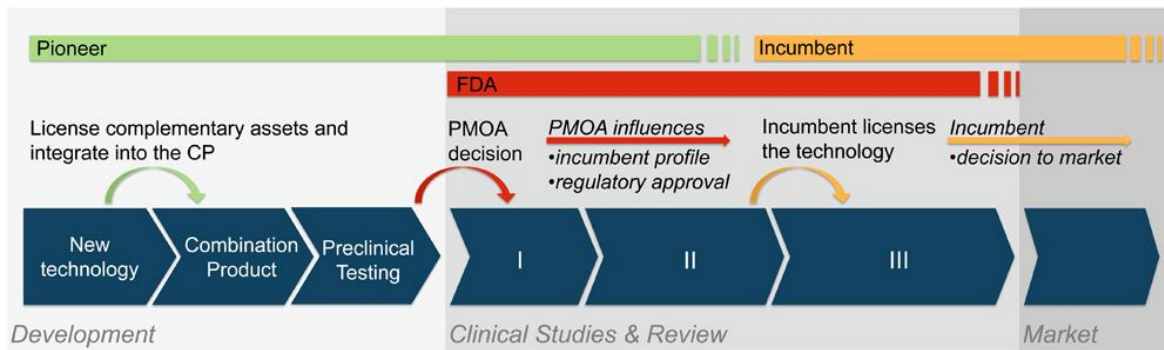


Figure 5



Graphical Abstract