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Where does the value of 'value-added' pharmaceuticals come from?

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The role of sound science, discovery, and innovation in value-added pharmaceuticals has not been sufficiently considered. This term is mainly used to define improved version of generic drugs. The concept of value-added pharmaceuticals has been picked up by different groups of companies, some are aiming to increase willingness to pay for their modified pharmaceutical products, others like generic pharmaceutical producers, try to become more innovative and less 'patent expiration-dependent'. Optimizing the existing pharmaceuticals can create competitive advantage and can strengthen the reputation and credibility of generic pharmaceutical companies.

Keywords: Competitive advantage, generic pharmaceuticals, innovation, value-added pharmaceuticals

There is an increasing confusion regarding 'value-added' pharmaceuticals. This term is mainly used to define improved versions of generic drugs. This paper discusses the 'value' of this improvement for generic pharmaceutical manufacturers. By launching such products, these companies attempt to become more innovative and less 'patent expiration-dependent'. Furthermore, adopting a patient-centric strategy as a framework for optimizing the modified pharmaceuticals can create value and can strengthen the reputation and credibility of the companies.

The role of sound science, discovery and innovation in 'value-added' pharmaceuticals has not been sufficiently considered. Moreover, the entire 'value' of 'innovation' has been excluded from some of the recent publications, and only commercial opportunities are encouraged and promised. The 'value-added' pharmaceuticals are not substitute products as we know them in marketing strategy. According to Porter's 5 forces in marketing research, substitute products are products that offer similar benefits to the consumer, threat of substitutes shapes the competitive structure of an industry. Value-added products, according to their economic definition, refer to 'extra' feature(s) of an item of interest (product, service) that go beyond the standard expectations and provide something 'more', even if the cost is higher to the client or purchaser. Value-added features give competitive edges to companies.

Where are we heading using these strategies? If 'innovation' is not considered and encouraged as a 'value', what can replace it to create a superior reputation for the generic pharmaceutical industry?

One of the recent publications [1] presented by Medicines for Europe (formerly European Generic medicines Association) discussed in details the value-added medicines. New indication, product expansion and drug repurposing require 'innovation' and discovery; 'value' can be created through this innovation and patient-centre business model, however, if only financial returns are considered and promised, the credibility of a company may be undermined.

The Medicines for Europe's report and other similar publications made us ask: In a rapidly changing pharmaceutical perspective, who will encourage and define a more innovation-focused

generic pharmaceutical industry? How to leverage the reputation of this industry? High quality innovative products are crucial for defining and creating a sustainable status and reputation.

Value-added pharmaceutical versions can also be considered as patient-friendly versions that are based on a patient-centric strategy. Patient-centric medicines are recognized as essential contributors to a patient's overall quality of life and life expectancy [2]. In addition to the selection of an appropriate type of pharmaceutical substance and strength for a particular indication in a patient, attention must be devoted to assuring adequate patient adherence and ensuring drug safety and effectiveness [2].

Patient-friendly pharmaceuticals may improve risk assessment, medication delivery, patients' and doctors' education, transparency, and adherence programmes.

Compared with non-innovative generic pharmaceutical products, the added value of innovative generic pharmaceuticals may provide improved transparency, superior quality and improved adherence. If the term 'value-added' is used as a nomenclature for products with higher commercial returns, then the whole value and significance of scientific attempts to provide patient-friendly pharmaceuticals will be lost.

The added value will differ depending on what needs to be added or improved in an existing pharmaceutical product.

The term 'value added' as a nomenclature for pharmaceutical products are differentiated pharmaceutical versions aimed at maintaining sustainability across alternative product portfolios [3].

Several medium-sized generic pharmaceutical companies have collaborated with academics and research centres to achieve sustainability.

However, innovation has not been considered as a strategic attempt as yet. Furthermore, product diversification has not been recognized as a crucial aspect for leveraging the reputation of the generic pharmaceutical industry to attain sustainability. Pharmaceutical treatments should 'treat' the illness and symptoms, relieve the pain, and reduce the harm. These attributes can create 'value'.

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When these concepts are misused or not clearly defined, they can even damage the reputation and long-term goals of a company.

The assessment of the value is required to advise healthcare authorities on the relative clinical and cost-effectiveness of treatments [4].

The 'refined therapeutics' concept is similar to the 'value-added' concept; it focuses on quality or improved quality rather than quantity.

Value added versus innovative, discovering new therapeutic applications for existing pharmaceuticals

Typically, 'value-added' versions emerge from strategic product portfolios and are used for product differentiation. The 'value-added' nomenclature is also used for hybrid/generic medicines¹.

Of the four-product differentiation strategies, evergreening, life cycle management (LCM) and extension strategies were used within the originator pharmaceutical companies, and the super generics/hybrids were used by the generic pharmaceutical companies [5, 6].

1. Evergreening strategy: Patent challenges, one of the major problems in the history of generic pharmaceutical industry, have been used to prevent competition from generics manufacturers [6]. The evergreening strategy extends the exclusivity, and various methods have been used by the originator pharmaceutical companies to achieve this exclusivity.

When combination drugs are launched by an originator pharmaceutical company, it can be considered as an 'evergreening' strategy, whereas those launched by a generic pharmaceutical company are aimed at transforming the classic generics business model.

2. Life cycle management: In LCM of branded pharmaceuticals, existing branded drugs are optimized or more mature molecules are altered.

However, whether the LCM strategy and tactics can reproduce successful outcomes everywhere remains unclear. The LCM strategy is based on pricing strategies and brand loyalty [7, 8].

3. Extension strategies: These include reformulation and repositioning of drugs and exploring new indications. Drug repurposing strategy, also referred to as re-profiling, reinvestigates the drug candidates that have not succeeded in advanced clinical trials because of reasons other than safety for potential new therapeutic applications. 'On-target repurposing' is a conservative approach in which the drug's known pharmacological mechanism is applied to a new therapeutic indication. Although this mechanism might be different from the original mechanism, it is known to share the same pharmacological fundamentals [9]. This strategy must not be confused with simple line extensions, for example, a cancer drug obtaining additional approvals for other types of cancer [4, 10].

4. Super generics/hybrids: For 10 years, a new wave of product innovation has been emerging in the generic pharmaceutical industry. These innovative activities included 're-innovated' products using new technology platforms, change in the managerial mindset, and evolving business models. These innovative approaches aimed to satisfy the patients' unmet medical needs [9, 11].

Most success stories about super generics and hybrids have emerged from small technology-based companies in which even a small income is highly considerable.

Super generics/hybrids can be improved versions of existing drugs, small molecule drugs offering a therapeutic advantage, drugs differing from 'me-too' generic drug products, dosage forms of patent-expired drugs improved by reformulation (often new delivery system), a novel combination of patent-expired drug substances, and products that are intermediate between new chemical entities and traditional generics, offering therapeutic advantage by addressing clinical or patient need.

A semantic shift has been observed in the nomenclature of super generics in the pharmaceutical literature. Labels such as 're-innovated products', 'value-added generics', 'new therapeutic entities', and 'enhanced therapeutics' indicate a subconscious search for a 'non-generic' identity and advancement from being simply a 'generic extension' [8].

The strategies used in generic pharmaceutical companies are different; value-added therapeutics focus on the 'therapeutic value' rather than the 'pure economic' value. This is a crucial investment for middle-sized generics companies, which consider this strategy 'worth doing' in order to completely differentiate their company.

The decreasing generics opportunities, the rising new technologies, new types of partnerships between academics and small drug delivery companies, value-based pricing, and new regulatory pressure have changed the landscape of the pharmaceutical industry for future investments.

The advent of personalized medicine and its associated demands for individualized products, in addition to the failure of the blockbuster model, have contributed to the changes within the entire pharmaceutical industry. We are advancing from a world where everyone receives the same treatment for a particular disease to a world of precision medicine where the profiles of individual patients are evaluated to eliminate the disease.

For satisfying the demands of this new paradigm, the next generation of drugs has to be highly safe and efficient and must satisfy unmet medical needs [9].

High quality, low risk, improved value-added therapeutics, and super generics/hybrids can ensure convenience, provide increasing patient adherence, efficiency, safety, sustainability, cost-effectiveness, competitiveness and innovativeness. Furthermore, these products can reduce the uncertainty about the timing and level of reimbursement decisions leading to uncertainty among stakeholders.

Value-added medicines/therapeutics are manufactured on the basis of a 're-innovation' framework [8]. This innovative design is an intermediate between incremental and radical innovation.²

¹Hybrid medicines are medicines whose authorization depends partly on the results of tests conducted on the reference medicine and partly on new data from clinical trials.

Hybrid medicines are formed when a manufacturer develops a generic medicine that is based on a reference medicine; however, this generic medicine has a different dosage strength or a different route of administration, such as through the oral route or through injections. Furthermore, hybrid medicines are formed when a manufacturer develops a medicine with a slightly different indication from the reference medicines. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/document_listing/document_listing_000335.jsp&mid=WC0b01ac0580514d5c

The importance of re-innovated drugs depends on several aspects:

1. Patient-friendly products with improved safety, adherence and services, and relevant pharmaceutical design aspects, such as selecting the route of administration, tablet size and shape, ease of opening the package, and the ability to read the user instructions or to follow the recommended (in-use) storage conditions [2].
2. 'Low risk' of development by applying advanced engineering and statistical methods to reduce the risk and improve risk assessment.
3. 'Low investment' through 'open innovation' and partnerships.
4. 'Faster time to market'.

These superior versions are improved, and these improvements can be made in terms of various aspects such as formulation, drug delivery system, combination and route of administration.

Optimizing pharmaceuticals and achieving financial returns

Despite their significance, refined pharmaceuticals are still described in a rather confusing manner. In the latest white paper published by Medicines for Europe, the value-added medicines were considered to be a type of drug repositioning, emerging either from combination drugs or reformulation, and an untapped product strategy promising more commercial returns for companies [1]. Drug repositioning can produce value-added pharmaceuticals, however, not all value-added pharmaceuticals are repositioned.

This paper tried to demonstrate the importance of 'value-added' medicines is due to their innovative characteristics, that innovation may bring into the market an opportunity for patients and health-care systems. 'Value-added' pharmaceuticals are contributing to drug discovery, some of them are winning product candidates for portfolio managers; others are new pharmaceutical treatments at accessible prices.

Value-added pharmaceuticals can develop a framework for satisfying the needs of patients that evolve with an increase in their age and the number of diseases. One of the advantages of value-added pharmaceuticals is sharing and receiving information on the value chain that could optimize the safety and effectiveness of drug therapy. Promoting collaborative scientific research in patient-centric drug product design will create real 'value' and nurture a sustainable reputation for the industry [12, 13].

Value-added pharmaceuticals are re-innovated and patient-friendly versions that can provide profitability for the manufacturers. The re-innovation strategy deals with the complexity in excipients and formulation, develops affordable medicines, optimizes drug quality and reliability, and uses new technological platforms. Integrating innovation in the portfolio of generics companies may create a new reputation for the generic pharmaceutical companies and maintain their market place.

²Product example 1: Aripiprazole (2 mg and 20 mg) tablets are hybrid generic medicines, which are similar to the reference medicine, Ability (5 mg) tablet (OTSUKA Pharmaceutical Europe Ltd); however, strength of the active substance in Aripiprazole (2 mg and 20 mg) is different from that in the reference medicine. (Aripiprazole is used to treat certain mental/mood disorders (such as bipolar disorder and schizophrenia). Available from: <https://www.otsuka-europe.com/>

Creativity and openness to innovation will be necessary to enter a new era of highly personalized and tailored medicines. A patient-friendly pharmaceutical product strategy will provide added value to optimized pharmaceutical treatments.

Value added medicines can be considered as a chance, but it will require a team effort by innovators, entrepreneurs, regulators, payers and policymakers [10-12].

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