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From generic to biosimilar drugs: why take an innovative pace?

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ORIGINAL RESEARCH

ABSTRACT

BACKGROUND: The transition of the generic/biotechnology industry to innovation by investing in innovative R&D will enhance business expertise in biopharmaceutical development and manufacturing. The major impact of this evolution is on patient access to treatment and savings for the health care systems. OBJECTIVES: The aim of this paper is to investigate the innovative aspect of biosimilar and biobetter products, manufactured by some big generic companies. We will also try to explore the innovative business strategy, implementing this high risk product differentiation policy. METHODS: This qualitative research is conducted by a series of interviews with CEOs, physicians, and academics in different countries. The qualitative data obtained were analyzed by Nvivo9.2 software. A literature review has also contributed to our key findings. RESULTS: The results show that switching into biosimilars/biobetters is an innovative strategic choice, approved by some big generic pharmaceutical companies. The biosimilar/biobetter products can be considered innovative because of their value added quality. CONCLUSION: Expanding the product portfolio to biosimilars/biobetter can be considered as a long run strategy in the innovative business plans aiming to ensure the market access. Patients and their access to better treatments are major components of these innovative business models.

Keywords

Generic Industry; Biosimilar; Product Innovation; Biobetter

INTRODUCTION

The changing role of the generic pharmaceutical industry has resulted into changes in the product portfolio by switching into more complex products like biosimilars and biobetters. Biosimilars (Europe) or "follow-on" biologics (USA) are biological products that are similar, but not identical, to an innovator product that is already marketed and whose patent has expired. Biosimilars cannot be considered "generic" equivalents of innovator products as they are not necessarily clinically interchangeable and in some cases may exhibit different therapeutic effects. It is critical that physicians and pharmacists truly understand the complex factors which apply to this new and challenging area.

The patent expiry of many biological drugs will open the door for greater numbers of biosimilar companies to enter the market, but marketing approval of biosimilars is a much more complicated issue than approval of generic equivalents. The clinical performance of biological treatments is highly dependent on the method of production and purification. Immunogenicity can be altered with different formulations or different manufacturing processes (that is, differences in host cells, purification and processing, formulation and packaging). Verifying similarity or comparability of a biosimilar with an innovator product therefore requires more than demonstrating bioequivalence, which is sufficient for conventional generic versions. The need for pharmacovigilance related to the biological treatments is an important issue following these manufacturing changes [1-3].

To date, the adoption of biosimilars by physicians and patients varies from country to country, reflecting local politics of pricing and reimbursement, the influence of stakeholders and their attitudes towards their use. Currently, Germany and France account for half of the biosimilars market value with 34% and 17% share, respectively, across Europe, although absorption in Spain and the UK has also begun to increase [4]. According to German IGES institute, the launch of biosimilar erythropoietin has allowed insurance funds to save €60 million due to price reductions in the first 12 months after their entry, the 60 million came from 2 sources: 40 million from originator price cuts and 20 million from biosimilar price cuts. The pre biosimilar market sales were 345M and this fell to 285 hence the 60 million is actual savings realized. A

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new study commissioned by Sandoz shows that, by 2020, eight countries in the European Union could save a cumulative total of between EUR 11.8 billion and 33.4 billion through the use of biosimilar medicines [5].

It is clear that biosimilars will become a major part of the biopharmaceutical market and will support patient access to pharmacotherapy. However, companies of biosimilar products do not follow the same industrial model as that of generic companies. The industrial model of classic generic companies is known as "copycat maker", but this model is being transformed. Generic pharmaceutical industry has tried to evolve through changes in their business plans and product portfolio with a view to maintain a sustainable market place. Differentiated products, offering a value-added quality, in a market of pharmaceuticals facing a lack of radical innovation, play an increasingly more prominent role.

The aim of this study is to analyze innovation around the development of biosimilars by generic companies. We will study the case of biosimilars from two points of views. First, from a viewpoint of relationship between generics and biosimilars, why can a switch into biosimilars be an attractive prospect? Second, from an innovative standpoint, are biosimilars and biobetters innovative products? The arrival of generic companies on the biosimilar and biobetter market may be the beginning of a new model where the pharmaceutical industry consolidates its presence around patient needs. Such a change could result in a profound renewal of the entire industrial chain, promote R&D and boost innovation [1,6,7]. By responding to all issues affecting the pharmaceutical sector, the change of the model, initiated by the new entrants could generate a new cycle of growth in the pharmaceutical industry.

METHODS

Data collection

In this study, we applied a qualitative approach. Semi-structured interviews were selected because they provide information collected during discussions with specialists about their views and experiences of recent changes. In the absence of research studies and documentation on this topic, we decided to launch discussions via social networks and conducted interviews as well as sending questionnaires by email. Until May 2012, 10 persons with different functions were interviewed in France, Belgium, Korea, Switzerland, United States, United Kingdom, and India.

Interviews were conducted with managers (M), industry consultants (C), lawyers (L), researchers (R) and physicians (P). Several economic and financial reports from Business Insight, Data Monitor, IMS, Ernest & Young, Markets and Research were also reviewed before and during the interviews. We have also participated in forums and conferences in Hungary, France and Germany to get up-to-date information. We also participated in webinars organized by international research centers such as Thomson Reuters. Discussion groups on the internet that have helped us include: Life Science Reimbursement Group, Management Change for Pharma, Biosimilars, Pharmaceutical Intellectual Property and Worldwide Generics, Biologics, Biosimilars and follow-on R&D. The interview time varied between 30 and 90 minutes.

Data analysis

We have prepared a database of our data collected from interviews. Interviews were recorded, transcribed verbatim and analyzed using the software NVivo9.2 software according to the Matrix Framework approach [8]. We used NVivo Dataset and survey to explore our findings. In practice, we coded raw data at nodes representing themes in our text-data. Alternatively, we ran text search query or word frequency to identify common subjects in survey responses before coding them. Framework matrices provided a way to condense the source data in a grid. Subsequently, we launched questions and found patterns based on our coding and checked for coding consistency among interviewees. This method helped us to compare results and to identify new perspectives of the survey results that could not be acquired without running the queries and coding the results. Our qualitative results indicated the main "nodes" in the classification results. The main results from the nodes are chosen according to our questions about the innovative portfolio of generic companies and their capacity to switch into biosimilars. Several child/sub-nodes relevant to the topic have been defined and added. The space covered by each node reflects the frequency of that node in our original database.

RESULTS

Figure 1 identifies the five major nodes resulting from the semi-structured interviews. In most interviews, the importance of the regulatory framework and the marketing strategy of the biosimilar industry in management decisions and its impact on the success in the pharmaceutical market were mentioned. The same general agreement on factors such as

"price pressure", "biosimilar price", "commercial viability", "innovative biosimilars", "barriers to entry of biosimilars" and the "importance of strategic marketing and sales force" has also been observed. Nodes and relationships between nodes are discussed in more detail in the following sections.

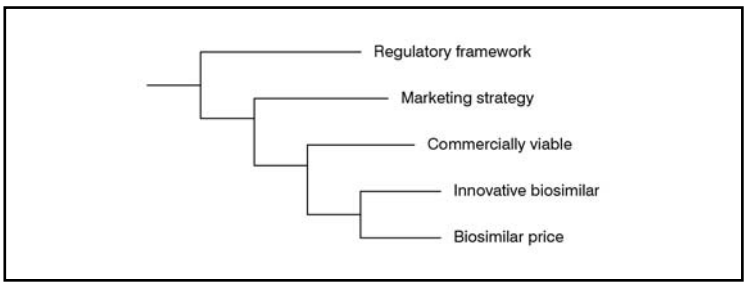

Figure 1. *Major nodes resulting from qualitative interviews*

From generic to biosimilar, a long way between imitation and innovation

Biosimilars differ from generic drugs by their characteristics, their raw materials and manufacturing processes. Differences between generics and biosimilars focus both on product development, marketing authorisation, and post-registration monitoring. Essential differences between the two regulatory pathways relating to biosimilars and generics are presented in Table I [9].

The price advantage is the main feature used by biosimilar companies to differentiate their products. According to survey results for Business Insights, «lower prices are a key marketing tool». However, price will not be the only way that biosimilars will seek to differentiate themselves from reference products. For instance, improved formulations and different methods of drug delivery are also very important features in the development of biosimilars (cfr. infra).

While national regulatory authorities in Europe are responsible for determining substitution policies, Member States that allow substitution of generic drugs generally have adopted guidelines that recommend the substitution between products with the same International Nonproprietary Names, and which are subject to the underlying principles of pharmaceutical and biological equivalence. However, substitution should not apply to drugs derived from biotechnology without knowledge and explicit consent of the physician. This approach was taken by French regulatory authorities. As biosimilars are not identical to the reference product, the substitution principle cannot automatically apply to biosimilars [1,10].

	Generics	Biosimilars
Description	Chemical origin. Same qualitative and quantitative composition as the active reference	Biological origin. Same physico-chemical, biological properties as the reference product
Duration of development	About 3 years	About 6-9 years
Development cost	0.5-3 millions dollars	40-80 millions dollars
Manufacturing process	Manufacturing processes of generic is the same as bioavailability	Biosimilar method of manufacturing differs from that of the reference product at several levels
Marketing authorisation dossier	Abbreviated Dossier. Data from bioequivalence and bioavailability	Complete application (Phase I and III (IV)). Comparative preclinical and clinical data in terms of quality, efficacy and safety versus the reference product
Therapeutic indication	All the indications of the originator are also indications of generic	Record indication by indication, and the need for setting up clinical trials for each of them if they are multiple, but exceptions exist
Substitution	Authorized	Not authorized
Reimbursement	Reimbursement rate identical to that of the originator	Reimbursement rate identical to that of the originator
Commercial promotion	Easier to implement and less expensive than the reference drug	Long and costly, is close to that originator

Table I. *Differences between regulatory pathways relating to biosimilars and generics*

From biosimilar to biobetter, an innovative evolution

Biosimilars are new versions of existing biopharmaceuticals following patent expiry. They are produced using the same core genetic material and are approved on the basis that they are comparable to the reference product in terms of quality, safety and efficacy. "Biosuperiors" or "biobetters" refer to a biological product that is similar to an already-approved biological product, but is also superior in one or more product characteristics. Product characteristics often targeted by biobetter applicants include longer product half-life in the body, lower likelihood of aggregation, greater efficacy, greater purity or fewer adverse events [11]. Table II sets out a number of differences between biosimilars and biobetters.

An expert in the United States gives the following definition of a biobetter: «As commonly used, the term biobetter is applied to any follow-on or next-generation product. In this respect, many or even the majority of marketed biopharmaceuticals are biobetters. This includes the vast majority of traditional biologics, particularly vaccines and blood/plasma products. And many follow-on (or ra-

ther me-too) recombinant proteins would now be viewed as "biobetters", such as the multiple follow-on versions of somatropin, insulin and Factor VIII biopharmaceuticals. Otherwise, historically, many recombinant proteins were biobetter versions of human tissue-derived protein products which they have often replaced» (P3).

Why are biobetters being developed by pharmaceutical companies? Biobetters allow companies to target an established mechanism, safety and efficacy profile, but generate sales of a new molecular entity and are protected by patents. Although development costs for biobetters are similar to that of a new biological product, chances of successful registration are significantly higher. This means that the business risk in developing a biobetter is significantly reduced, and the potential for return on investment for a company is greatly improved [11,12].

Nevertheless, Table III shows that biobetter and biosimilar products which aim to be innovative may face several challenges like: the uncertainty on financial returns (commercial viability), technical and manufacturing problems, a professional approach to marketing and sales force, price differential and innovativeness of the product.

Biobetters are value-added biosimilars, but this requires clarification as to what "better" means? Here, we hear from an American expert: «I firmly believe that biosimilars can be better, that means they are not equal as margins of tolerance apply, which are commonly accepted. The scope of those margins require "justification" which I deem is a loophole (for the EMA) to assess the product on a case by case basis» (M2, June 2012).

Yet, there are very different ideas about biobetters, the major problem being in the regulatory definition: «In a U.S. regulatory context**,** biobetter is defined as including (there could be other ways of qualifying) the same biologic (fully biogeneric, fully identical in all active agent and formulation aspects), but with something else that is different and that is presumed to be an improvement. There is no "variant" of a reference product involved here. For example, this could include the "biobetter" being the absolute same product but marketed by a different company holding its own full approval and with its labeling including an additional or broader indication». (C3, USA).

Beside the regulatory problems for biosimilars and biobetters, the patient's point of view remains another challenge:

- «The concern in the patient's mind is the fear of being prescribed an inferior product, especially when this is thought of as a cost-saving measure. The more data we have to dispel the inferiority theory, the more likely we will be successful in prescribing biosimilars, so the answer is data, data, data» (P1, Oncologist, Michigan).
- «Is the drug as good as the branded option? Are there unknown potential side effects related to poor manufacturing practices? Where is the drug made? Industry could help by assuring the patient of the "purity" of their product» (Rheumatologist, Northwest United States).
- «They will be concerned about safety and efficacy. It will be easier to reassure them if each claimed indication for a biosimilar is established through well-performed clinical trials. The industry can help by sponsoring and supporting these trials». (P2 Oncologist, New Jersey) [13].
- «As for the drugs from the perspective of patients, I think biosimilars will be just as effective and perhaps even more safe (cleaner; use of newer technology). Remember that the major entrant to the biosimilars market in the USA and Europe are big players with wealths of experience» (M4).

Why can biosimilars and biobetters be innovative products?

Although the concept of biobetters is just emerging, there are certain companies that have successfully redesigned existing products to create better biosimilars or biobetters [14]. The innovative value and benefits of using biobetters include lower dosage, re-

	Price	Regulation	Approval	R&D	Marketing	Communication
Biosimilar	Reduced price	Is also a regulatory title	Clear requirements for approval	Substantial R&D costs	Requires professional marketing and sales force, faces aggressive lobbying and litigation	Lack of information and communication for demand side (patients and prescribers)
Biobetter	Higher prices	Is a legal definition	Lack of clarity	Lower R&D costs, 12 years of market protection	Professional marketing and sales force are needed	

Table II. *Specifications of biosimilars and biobetters*

	Commercially viable (%)	Manufacturing (%)	Marketing strategy (%)	Cost-effective alternative (%)	Price differential (%)	Superiority of biobetter (%)
Biosimilar innovation	35.02	33.33	31.77	33.33	33.33	31.4
Second generation product	32.49	33.33	31.77	33.33	33.33	31.4
Biobetter	32.49	33.33	36.45	33.33	33.33	37.2

Table III. *Challenges faced by biobetter products*

duced side-effects, reduced rate of degradation in the blood stream and reduced risk of immunogenecity. In discussions with Americans, the focus is on technical and technological innovation:

- «A longer half-life can be obtained by different conjugation chemistries like pegylations, albumination, Fc conjugation, polysialylation, hessylation, hepylation, etc. Among different chemistries, pegylation is most common approach currently used for biobetter development. A number of biological drugs developed by pegylation of existing biologic molecules are available in the market, e.g. pegylated G-CSF (Neulasta®), pegylated EPO (Mircera®), pegylated interferon-α2a (Pegasys®) etc.» (M5)
- However, the innovative value and benefits of biobetters may come at a price: «There might be this misconception that reduced R&D costs will translate into reduced pricing of drugs, but that is not the case. The idea of biobetters is not that they are cheaply priced. They cost up to 120-150 percent of the innovator brands unlike biosimilars, which are sold at less than 50 percent of the innovator brand price» (C5).
- «A moderately superior biobetter can obtain 20-30 percent of market share whereas four biosimilars can probably achieve about 50 percent of the market» (M6).

Creating differentiation

Can a biobetter overcome competition from biosimilars and establish a niche segment for itself? Multinational companies always looked at replacing their blockbuster drugs once they lost exclusivity. However, during the last decade with low innovation rate, the industry has seen various innovative business models. Similarly, in biologics we have seen the growing influence of follow-up drugs once a novel biologic loses exclusivity. To combat this threat, biobetters are regarded as the "game changer" once the originators lose patent rights [6,7]. Some generic companies do not merely wish to be a "me too" drug company. This new generation of generic companies has realized that they have to innovate in order to create market space for themselves [6].

DISCUSSION

Biosimilars and biobetters are a new business opportunity for pharmaceutical companies. This business model seems to be driven by the lack of innovation in product portfolios, price pressure, competition and industrial evolution. Our qualitative study has shown that investing in the production of biosimilars/biobetters is an innovative approach for generic companies. This is because the development of biosimilar/biobetter products requires advances in scientific and analytic techniques that provide greater ability to characterize and compare complex molecules. Also, the product differentiation approach seems innovative because these products cannot be manufactured without technical, scientific, economic and commercial innovation, and because the entry of generic companies on the biosimilar/biobetter market is likely to stimulate competition and innovation dynamics.

Switching to biosimilars/biobetters is not an easy, minimum risk strategy but a decision that requires considerable technical, scientific and financial investment in a long-term perspective. However, it should be noted that these products are innovative and that biosimilars/biobetters can contribute to society through cost reduction, better access and high-quality treatment. The development of the biosimilar/biobetter business is therefore a source of growth, providing new sources of revenue, margins and opportunities for product differentiation.

The transition by the generic/biotechnology industry to innovation by investing in innovative R&D will enhance business expertise in biopharmaceutical development and manufacturing. Even if biosimilars/biobetters are a source of innovation, their development is facing several challenges: unclear regulatory frameworks, absence of substitution policy, prescriber

and patient resistance will slow down their adoption.

Profitability from the sale of biosimilars/biobetters is likely to be limited in the short term, given the high investment costs and long development times. In response to this, companies need to have strongly integrated R&D, production, sales and marketing processes. Access to sales and marketing capabilities can be achieved through collaborations between pharmaceutical companies and specialty biotechnology firms with technical expertise.

Lack of communication and misinformation are still key problems in moving biosimilars/biobetters forward in Europe and the United States. Effective sales communication will promote greater market share of biosimilars/biobetters. Education and communication campaigns are also necessary to give unbiased information to patients and health professionals.

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