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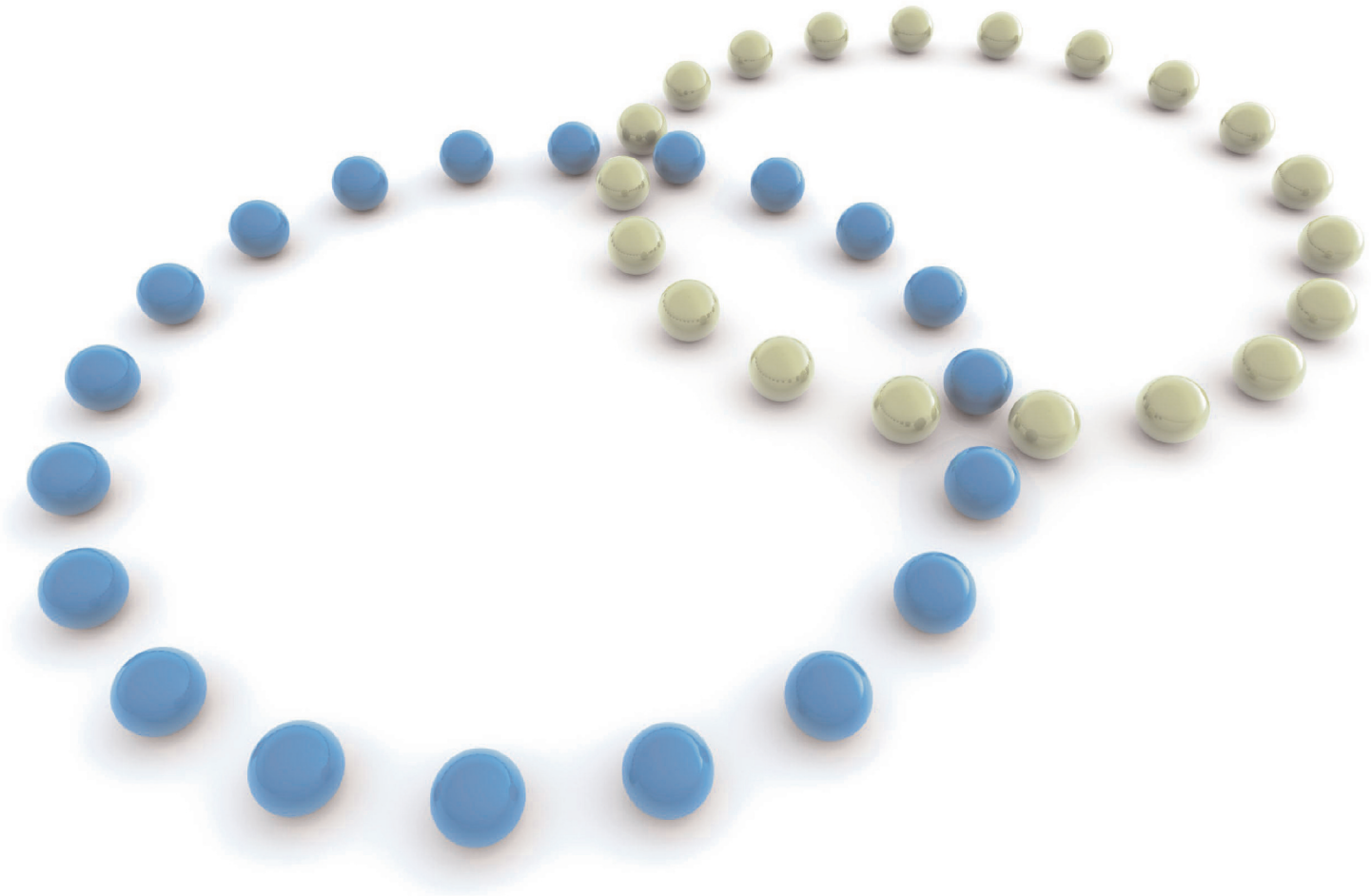
Generic Medicines: Essential contributors to the long-term health of society

SECTOR SUSTAINABILITY CHALLENGES IN EUROPE



Generic Medicines: Essential contributors to the long-term health of society

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EXECUTIVE SUMMARY

Sustainability has been defined as the capacity to withstand, endure, nurture and prolong over time. An ability to continue that should not be confused with simply surviving, but rather maintaining the vitality and strength to build on, enhance, and thrive.

Today, generic medicines play an essential role in treating disease by increasing the accessibility and affordability of modern day pharmaceuticals in global healthcare systems. The sustainability of the generic medicines sector is vital to ensure that these benefits accrue into the future and essential medicines continue to be made available to as many patients as possible without deference to cost.

The benefits of a healthy and dynamic generic medicines industry – historically and in the future - are evident. Currently over half of the volume of medicines are supplied as generics medicines but this represents just 18% in value terms. The EGA have estimated that, to date, generics medicines in the EU have generated savings in the order of €30 billion, excluding those made from the stimulation of competition with the pharmaceutical sector as a whole. However, with the expansion of the European Union to 27 member states, the accrued savings could certainly be projected to double this figure. Any activity that curbs the role of generic medicines could have disastrous consequences, not only for generics manufacturers but also, more especially, for patients, as well as governments, payers and all other stakeholders involved in the delivery of healthcare.

The long-term sustainability of the generic medicines sector relies on fair prices and a level playing field. Acceptable margins across the entire generic medicines supply chain will be essential if their full value is to be realised. The recent paper *'How to Increase Patient Access to Generic Medicines in European Healthcare Systems'* from the EGA Health Economics Committee highlights the importance of increasing patient access to generic medicines and the benefits to be gained from their faster uptake[1]. Treating them solely as a cost-saving mechanism will serve only to stifle their ability to deliver continued benefits long-term.

In certain countries, particularly where the generic medicines market is well developed, there are a high number of generic medicines companies, thus ensuring healthy competition. Often there is a mix of large international players and local producers. This is a key benefit for smaller generic medicines markets which rely on a local presence to ensure a supply of medicines that would not otherwise be available from outside the country due to low volumes or other issues. Europe is becoming increasingly dependent on a high percentage of imported generic medicines. Without the appropriate level of control and monitoring, this could easily lead to shortages and problems with supply continuity in those smaller markets.

Globalisation of the generic medicines industry will bring new challenges to Europe which must be met if the sector is not to be marginalised with respect to both pricing and supply.

Innovation has been traditionally perceived as the domain of the research-based originator companies. However, generic medicine companies often spend significant sums on innovating – improving formulations, enhancing delivery systems and finding solutions to patient compliance issues. In 2007, 7% of revenues from the generics medicine industry were spent on research and development alone. Furthermore, sector investments in manufacturing and development facilities have created a solid base of employment (150,000 direct employees in the EU[2]) yielding societal benefits that go beyond the realms of healthcare.

The potential benefits of the generics medicine industry will not be maximised if the focus is on the lowest price alone. There is a need to increase the volume of generic medicines penetration in the EU market and optimise such key areas as competition with in-patent medicines, co-payment policies, time to market, and ready supply. A generic medicine treatment is now available within many of the major therapeutic classes and this is often the 'gold standard' option for specific diseases. Opportunities exist to recommend schedules that encourage initiation of treatment with these 'gold standard' generic medicines. This is a positive sign which should increase the uptake of these drugs and potentially generate long-term savings through the use of a safe and effective therapy at an affordable price.

THE RISING COSTS OF HEALTHCARE IN EUROPE

The provision of an effective and efficient healthcare system in any country is a complex equation balancing appropriate levels of patient care with resources available. Within this lies the need for infrastructures to support both primary and secondary care as well as associated services such as social welfare.

Making direct comparisons of costs and best practices across EU member states is difficult; inherent political differences give rise to highly variable systems. No one country is the same. However, one element that is common to all and often the focus of attention is the cost of medicines.

[1] How to Increase Patient Access to Generic Medicines in European Healthcare Systems: A Report by the EGA Health Economics Committee. Frank Bongers, Hugo Carradinha, June 2009. [2] EGA.

Although medicines generally constitute only around 10% of a country's total healthcare budget (with generic medicines only comprising between 1-2%) they are a prime target for cost savings - despite being arguably the most cost-effective part of the healthcare solution. However, even here, the lack of coherent policies and variations in pricing and reimbursement systems, socio-demographics and the management of healthcare within each EU member state make comparisons difficult. What works in one country may be totally inappropriate in another.

One thing is certain, the ageing population and changes in lifestyle automatically bring an increased demand for healthcare and consequent escalation of costs. Pharmaceutical expenditure has been growing at comparable rates across all the major Western markets (Figure 1), with the developing markets exhibiting greater growth due to expanding access to medicines.

FIGURE 1. Top 10 markets pharmaceutical sales and growth. Audited markets in MAT Mar 2009.

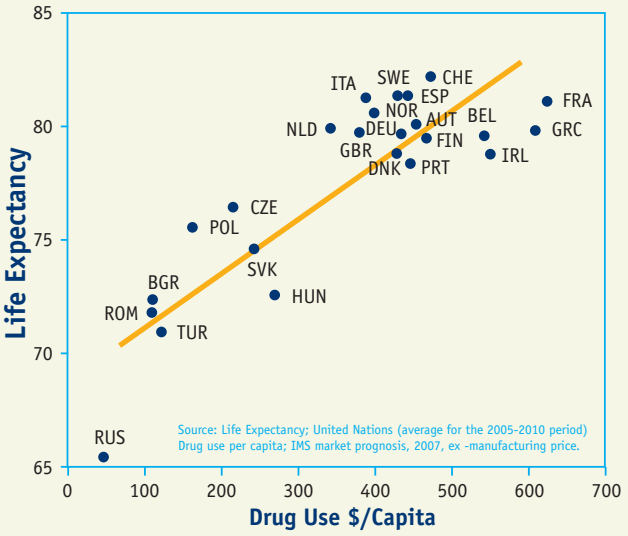
COUNTRY	US$bn 2009	% Mkt Shr 2009	% Growth Const US$ 2009	CAGR 04-08
10 Key Markets	$560.6	77.7%	3.8	5.9
United States	288.5	40.0	2.4	6.3
Japan	71.6	9.9	3.0	3.0
France	41.0	5.7	2.1	5.4
Germany	40.1	5.6	4.2	4.1
Italy	25.7	3.6	3.9	4.1
Spain	22.0	3.0	7.7	8.0
United Kingdom	20.9	2.9	4.1	3.1
China	20.8	2.9	25.2	22.0
Canada	18.0	2.5	5.8	8.1
Brazil	12.0	1.7	11.9	11.6

Source: IMS Health, MIDAS, MAT Mar 2009

Prolonged life expectancy in diseases previously associated with high mortality is also extending the use of longer-term chronic therapy treatments, further increasing the burden on healthcare providers. It is a fundamental principle in medicine that pharmaceuticals can delay or even prevent the need for costly hospitalisation in some patients. Therapies to improve quality of life in patients with terminal diseases are also playing a growing role in the physicians' armamentarium.

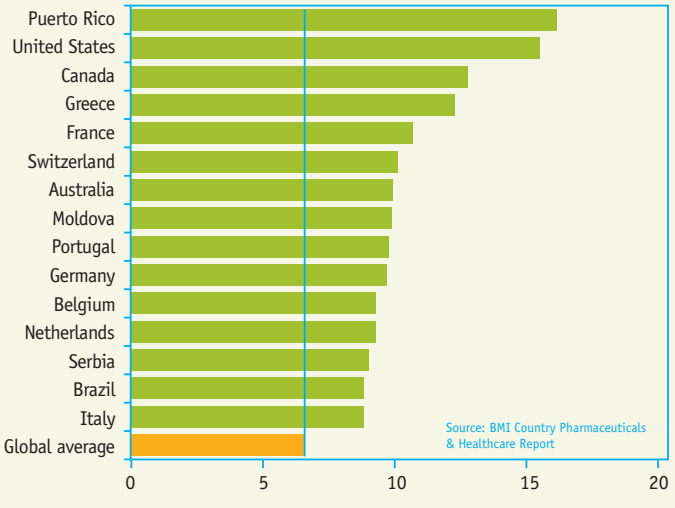
Against this background, it is possible to draw a correlation between life expectancy and pharmaceutical consumption as shown in Figure 2.

FIGURE 2. Link between drug use and life expectancy in an ageing Europe (2005-2010).



Pharmaceuticals undeniably play an essential role in improving and maintaining health, but managing and controlling cost remains a major challenge for society, including governments and payers. Although the percentage of GDP spent on healthcare is fairly consistent in the major EU countries (Figure 3), the absolute amounts available are straining to deliver the desired levels of healthcare.

FIGURE 3. Top 15 Countries According To Healthcare Spending in 2008 as a % of GDP.



COST AND AFFORDABILITY

A successful and innovative pharmaceutical industry brings many benefits. However, these have to be balanced with affordability and external competitive forces in order to provide the appropriate standards of healthcare. It can be argued that the majority of illnesses now have gold standards of therapy available with which patients can be adequately, and successfully, managed. However, there still remain significant unmet clinical needs where the search for new or improved medicines continues.

Certain clinical challenges require medicines based on biotechnologies, which are associated with higher research and development costs. In order to recoup the increased investment, and in part because they are generally intended for a smaller population base, these medicines are often associated with a premium price.

At the same time, development costs for the generic medicines industry are also rising, due to both the increasing complexity of the molecules that are losing protection and the rising burden of regulatory requirements.

It is vital that patients have access to the most appropriate medicines available in order to avoid the longer-term morbidity issues that can arise from non-treatment. Improved access to medicines through affordable generic medicines provides a solution in many therapeutic areas, and policies should be based not only on cost but also on clinical value.

Generic medicines not only offer cost savings but also the ability to ensure that patients continue to receive those gold standard treatments at affordable prices post patent expiry.

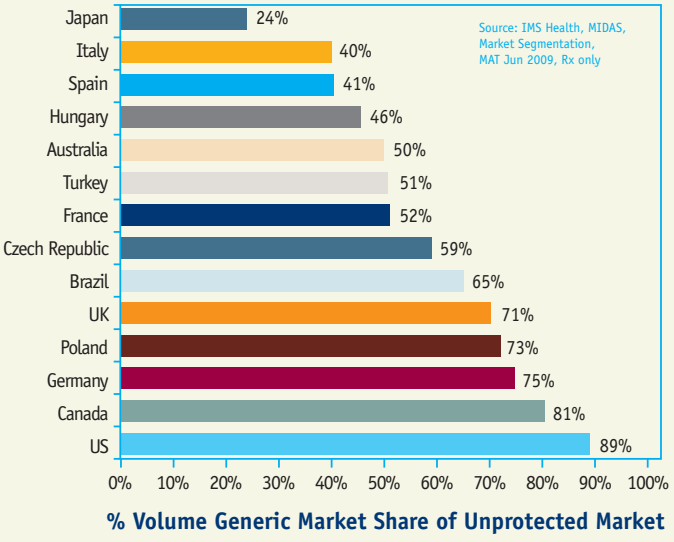
The growing cost of healthcare is unavoidable in today's climate; drug expenditure is forecast to increase by around 5% annually over the next 3-5 years. A long-term approach involving increased utilisation of generic medicines could compensate for some of this rising expenditure without compromising outcomes. In his 2006 paper on sustaining generic medicines markets in Europe[3], Prof. Dr. Steven Simoens underscored the necessity for policy intervention to secure the development of a competitive generic medicines market. However, different measures will need to reinforce each other and be part of a coherent generic medicines policy. For this to happen, strategies must be planned and implemented now.

ROLE AND CONTRIBUTION OF THE GENERIC MEDICINES SECTOR

The role of generic medicines has been to provide essential medicines that are both high quality and affordable throughout the EU. There can be no doubt that their use has increased patient accessibility to medicines and provided significant savings for EU healthcare systems – savings that can, among other things, be deployed to cover the costs of newer, innovative, and generally more expensive medicines that truly add increased clinical benefit if managed effectively.

Due to the differences already noted in pricing and reimbursement systems across Europe it is difficult to accurately project the savings from generic medicines. To a large extent, the magnitude is dependent on the level of utilisation in each country (Figure 4) and the price differentials between them and the originator brand. In the USA, for example, where the use of generics is almost 90% within the off-patent (unprotected) market, savings from their use in 2008 alone totalled US$121 billion. It can be argued that potential savings in many European countries are not fully exploited due to lower utilisation of generic medicines in key therapy areas.

FIGURE 4. Utilisation of generic medicines within the unprotected markets.



The significant contribution arising from the efficient use of generic medicine policies within certain countries cannot be denied. The scope for further savings is dependent on a sustainable generic medicines industry and policy supported by governments, stakeholders and patients.

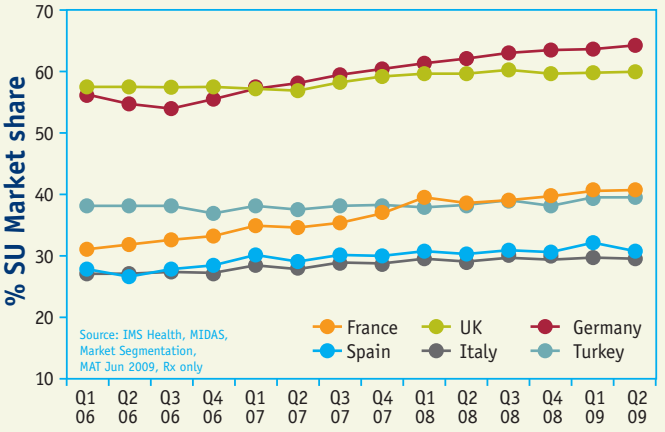
[3] Professor Dr Steven Simoens, Sustaining Generic Medicines Market in Europe, Katholieke Universiteit Leuven, April 2006.

VOLUME PENETRATION AND PATIENT ACCESS

When considered as a proportion of total pharmaceutical consumption within a given country, the volume consumption of generic medicines in the EU is at an even lower level, and highly variable across countries (Figure 5). In the most developed generic medicines markets, such as the UK and Germany, their volume use represents more than half of the total market. However, in less mature generic medicines markets, such as Spain and Italy, volumes remain low. Thus, in order to deliver the full benefits of generic medicines, greater importance must be placed on increasing volume use rather than focusing simply on price. Introducing educational programmes for prescribers, dispensers and patients, to demonstrate the benefits of treatment regimens incorporating generic medicines, could be one useful way of achieving this.

Reducing the price of generic medicines in low volume markets can severely challenge the sector's sustainability. In these countries the cost of maintaining the essential infrastructure related to registration costs, pharmacovigilance and other legal requirements will not be covered by the revenues generated. More affordable and lower-priced treatments will be a natural result of increasing the demand for generic medicines and will raise the level of competition in all markets.

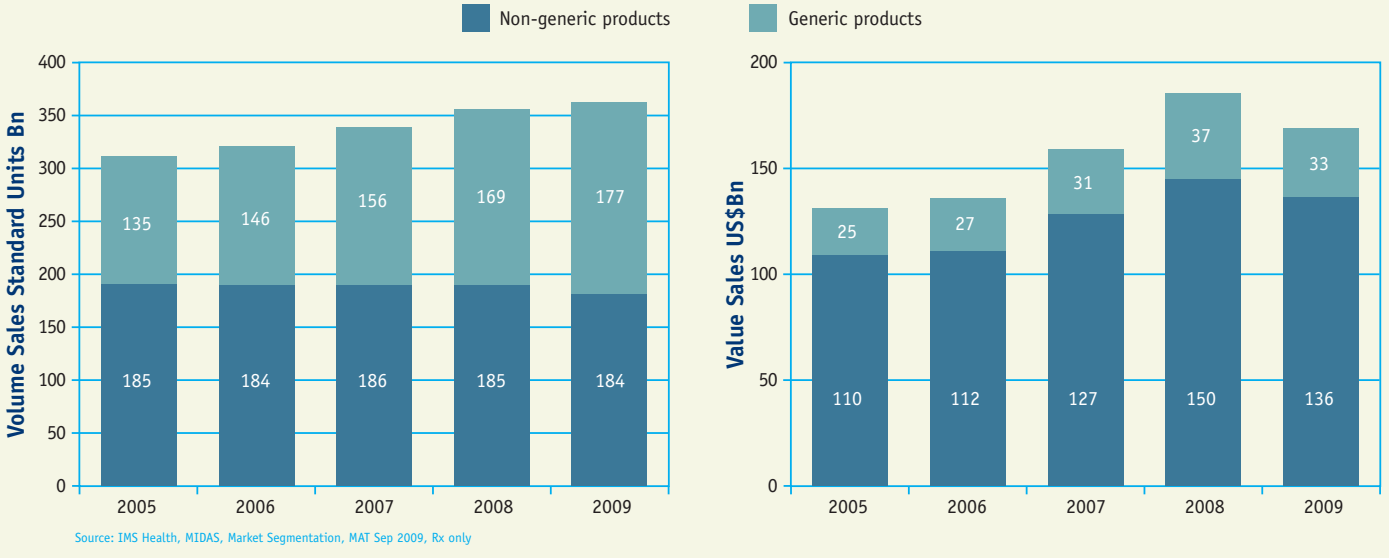
FIGURE 5. Contrasting generic medicines volume penetration in key countries.



VALUE GROWTH AND AFFORDABILITY

Although generic medicines now fulfil over 50% of the demand for medicines in Europe, they still only represent 18% of the total medicines bill. Value growth in the sector is the result of new generic medicines entering the market following patent expiries in the absence of any price increases. Indeed, significant price decreases on many molecules in the major markets, arising from competition or enforced pricing policy changes, has countered value growth each year (Figure 6).

FIGURE 6. In Europe, generics make up almost one half of volume sales, but merely a fraction of value sales.



[4] Final report on the EU Pharmaceutical Sector Inquiry 2008/09. Accessed http://ec.europa.eu/competition/sectors/pharmaceuticals/inquiry/communication_en.pdf

KEY FACTORS FOR AN EFFICIENT GENERIC MEDICINES MARKET

To maximize the contribution of generic medicines to the affordability and sustainability of the healthcare system, the generic medicines industry must be able to operate within a sustainable, competitive and efficient market model. In order to derive the maximum benefit from a generic medicine it must be available from day one following patent expiry. This may seem obvious. However, in certain markets, generic medicine entry is often delayed, partly by the need to gain pricing and reimbursement approval. Depending on the sales value of the originator product, lost savings can amount to tens of millions of Euros within the first year. In its final report on the EU Pharmaceutical Sector Inquiry (2008/9) the European Commission suggested that the additional savings on the 219 prescription medicines investigated could have been as much as 20% higher if there had been no delays to entry[4].

As noted earlier, pricing systems in each country vary widely. Some directly link the price of the generic medicine to the originator price whereas others have 'dynamic freedom' of pricing and leave it to competitive market forces to dictate prices. Whatever the system, the potential savings are significant; accrued benefits over the years from generic medicines are estimated to be in excess of €100 billion in the major EU markets.

HEALTHY COMPETITION

Stimulating competition between generic manufacturers not only means lower costs for patients but also drives product improvements, distribution efficiencies and improved access to all medicines. Whereas an originator product usually comes from a single source, generic medicines are typically multi-sourced, with several generic medicine manufacturers producing the same product. This generally assists continuity of supply for particular medicines which can be important at times of increased demand, such as unexpected requirements for anti-infectives during an influenza epidemic.

SUPPLY CONTINUITY

A further benefit of generic medicines arises from the sector's continual provision of products many years after the patent has expired. The originator may have exited from the market for several reasons after loss of patent protection but invariably because of low volume demand leading to limited commercial opportunity. It is often the generic medicine that remains on the market, meeting the needs of patients for whom there may be no suitable therapeutic alternative for their particular condition.

ESSENTIAL INVESTMENT

Investment and employment within the generic medicines sector is vital for some member states. It is estimated that the European generic medicines industry consists of more than 700 companies directly employing around 150,000 people. Research from the largest generic medicines employer in Germany has shown that although they 'only' employ 1,300 staff, by doing so they create a further 2,000 jobs locally and in the region of another 1,400 jobs nationally. In economic terms, through direct spending, they generated "value-added" benefits in 2008 of approximately €140 million locally or about €243 million nationwide. A careful extrapolation of this value would indicate that the European generics industry represents significant economic value within the community.

In some cases, it is the local generic medicines industry that sustains employment in a country's pharmaceutical manufacturing sector as originator products are often imported from a central manufacturing site. Consolidation within the generic medicines industry is threatening this position but countries with low-cost manufacturing potential may benefit, as well as those companies that are able to identify niche or local country-specific opportunities.

CHALLENGES TO THE EUROPEAN GENERIC MEDICINES INDUSTRY

Some of the major challenges to the generic medicines industry in Europe arise from increasing costs in a market undergoing constant price erosion, unsustainable policies and an unequal playing field compared to other geographical regions with regard to taxes, regulations and incentives. All of these limit the competitiveness and sustainability of the European generics sector.

LIMITATIONS ON PRE-EMPTING PATENT EXPIRY

The introduction of the Bolar provision in Europe[5] has now enabled European manufacturers to develop generic medicines within Europe prior to patent expiry. Previously, this could only happen in certain countries where different patent positions or non-observance or non-existence of patents made it possible.

Notwithstanding this advance, certain restrictions still inhibit such development within Europe - the main one being the manufacture of commercial batches within the EU prior to patent expiry. As a result, products developed and manufactured in those 'non-patent' position countries can be on the market earlier than any product manufactured in Europe – a position that is achieved by importing finished product on the day of patent expiry having already gained approval for its release using samples from the commercial batches. For European generic medicine companies this has meant continually having to develop many key molecules

[5] Directive 2004/27/EC: An exception to patent infringement for obtaining EU marketing authorization of a generic or similar medicinal product.

outside the EU – including manufacturing which must take place in the same country as product development to meet the day one launch.

Generally speaking, products are manufactured where they are developed because of the need to link the regulatory dossier with the site of manufacture. Although not a barrier this does add a further hurdle of complex logistics.

Allowing the manufacture of commercial quantities in the EU prior to patent expiry, ready to launch on day one following loss of exclusivity, would encourage the development and manufacture of more generic medicines within Europe – and avoid the delays and missed opportunities for manufacturers and healthcare providers.

IMPORTATION

Importation into Europe poses few major hurdles for overseas generic medicines manufacturers. Conversely, exporting into these markets is often far less favourable given the strong incentives that exist for the local industry - including export subsidies, tax breaks and grants for building production or development facilities. Indeed, many European companies are starting to take advantage of these benefits to the detriment of investments in Europe.

INCREASINGLY STRINGENT REGULATIONS

The generic medicines industry also faces an increasing regulatory burden such as pharmacovigilance requirements, periodic safety updates (PSURs) and the introduction of Braille packaging. Rising costs in quality assurance, anti-counterfeit measures and product security are also a major challenge and must all be absorbed without the ability to counter them with price adjustments. Regulatory authorities gather around 70% of their income from generic medicine manufacturers, reflecting not only the multiplicity of submissions for the same molecule but also the numerous variations they are required to submit.

COSTS AND PRICING

In most instances, manufacturing cost levels for generic medicines are the same as those for an originator product. Often, the only flexible parameter for reducing costs lies within the price of the active pharmaceutical ingredient (API) which may fall over time as API manufacturers face their own competition. All other costs tend to be fixed, with little room for manoeuvrability. This is the reason why any downward pricing adjustment by an originator company prior to generic entry creates problems for the generic medicines manufacturer. In this instance, any price linkage requiring the generic medicine to be set at a permanent fixed percentage discount to the originator will seriously disadvantage its introduction and financial viability.

Initial price linkage may be necessary but should not be continued throughout the lifecycle of a generic medicine as it can be a major barrier for products with high development costs and relatively slow product uptake. This includes, for example, biosimilars or products with a 'narrow therapeutic index'. As prices sink ever lower, the sustainability of some molecules in certain markets becomes increasingly questionable.

In most countries, legislation only allows reimbursement prices to go down and this becomes an issue with infrastructure costs such as salaries and energy costs increasing year-on-year. In this event the conflict becomes self-perpetuating.

Pharmaceutical markets in the EU are national, each with their own drivers and systems. Some member states are taking steps to learn from other healthcare systems with a view to adopting them in their own country. However, it is important to remember that what works in one country may not yield the same benefits in another. Systems are not always compatible with the basic healthcare infrastructures in other countries. If all countries were to adopt the lowest price approach, sustaining the current supply of generic medicines in all countries would be a major challenge.

TENDERING

In this respect, one major threat to the generic medicines industry is a change in the procurement method for generic medicines. Fragile systems have been disturbed since elements of tendering were adopted in Denmark, Germany and the Netherlands, producing what may only be considered as some short-term savings. This has also had some unsettling financial effects regarding the stability of some pharmacists and wholesalers as well as problems with continuity of supply as seen in the Netherlands and Germany

From the generic medicines manufacturers' position the impact of tendering in the long-term could lead to major changes in the industry, including reduced investment in not only the more complex molecules and biosimilars but all prospective new generic medicines - especially more traditional molecules which may have a lower market value. Few companies could afford to run the risk of committing large sums only to find themselves unable to recoup their investments or left with large inventories if they are not awarded a supply contract upon approval.

There is continued interest in the European generic medicines market from the Indian and Chinese-based industry. These countries see Europe as an opportunity to fully utilise their manufacturing capacity for finished dose forms and APIs at marginal cost. This places the European-based industry at a severe disadvantage as it is often the low cost overseas players that are able to drive down prices and maximise their market share through tendering, which requires little European infrastructure.

BIOSIMILARS

The next category of products considered most likely to generate significant savings will be biosimilar medicines. Products derived from biotechnology are among the fastest-growing medicines and often considered expensive. If savings are to be generated, there is a need for early clarification of the regulatory approval pathway for biosimilar products. Although Europe is seen to lead the way here, there is still uncertainty around complex, large molecules e.g. monoclonal antibodies. More transparent requirements would not only speed their development but also encourage more companies to invest, raising competition in this very important market sector.

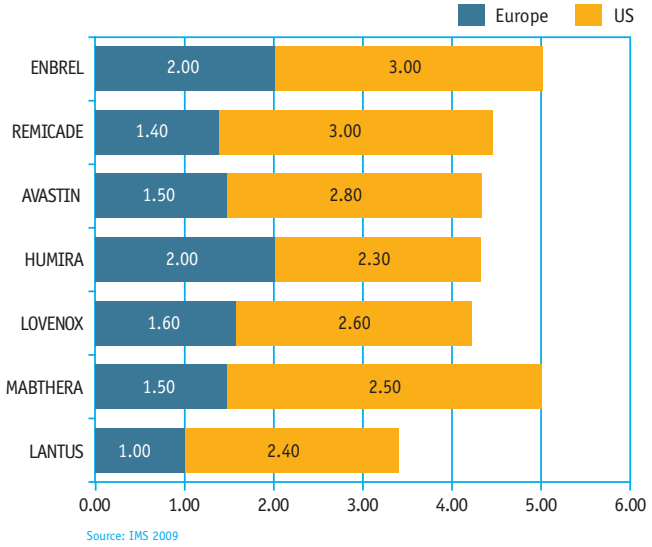
Biosimilar approvals are based on stringent submission requirements, including substantial clinical studies. Accordingly, their associated development costs are significantly higher than for small molecule generic medicines; estimates range up to US$150 million for each molecule. Additional high-cost risk management plans must also be produced and implemented. Global development programs for biosimilar products are also a must; not even large, financially healthy companies can afford to duplicate such expensive pre-clinical and clinical studies in each country or region in the world. There is also a clear need to develop a consistent scientific global approach to regulating these products.

As a novel segment, biosimilar medicines are proving a challenge to bring to market. In addition to the high costs of development, unfamiliarity with the product class and misinformation has created a significant need for promotion. Furthermore, with lack of clarity around their inter-changeability and substitution with the originator reference product they have been generally slow to gain market share.

The ability of the biosimilar medicines' company to recoup this investment is vital to secure the development of second generation biosimilars and achievement of the full value and savings they can bring.

Products based on biotechnology are indeed significant contributors to the rising cost of the drugs bill in all countries. Savings from traditional generic medicines will not be able to compensate for this escalation in drug expenditure, with the resultant inability of payers to control costs. Increased competition and market penetration of biosimilar medicines provide a major opportunity to control the costs and availability of biopharmaceutical medicines. It is estimated that a 20% price reduction could result in savings in excess of €1.8 billion.

FIGURE 7. Biopharmaceuticals with High Biosimilar Market Potential – Top 6 Biopharmaceuticals, in bn USD (2009).



Source: IMS 2009

DELAYING TACTICS

The recent EU Pharmaceutical Sector Inquiry highlighted the issue of practices employed to delay or even block the entry of generic medicine competition. Instruments used by the originator companies concerning the products reviewed were found to have delayed entry by more than seven months post loss of exclusivity (LoE).

The use of patent clusters - allowing a medicine to be protected by up to 1,300 patents or patents pending - leads to a lack of transparency for the generic medicine developer. The ensuing litigation can take several years (on average 2.8 years in the Inquiry report) and be a costly exercise for the generic medicine company. This cost will eventually have to be passed on to the payer or patient through pricing, which again erodes the potential saving from the generic medicine. Furthermore, in 75% of the European Patent Office opposition cases started by generic medicine companies, patents are revoked or restricted. Interventions before competent authorities, based on patent linkage or claims of minor quality, have delayed the generic medicines market entry on average by four months.

Generics won 62% of the 149 litigations that proceeded to trial. Of the 700 total started litigations, 223 were settled, with 50% of those settlement agreements containing what the Commission consider to be a limitation on generic entry. Some were associated with a direct payment from the originator company or a license and distribution agreement.

The threat of litigation is, for some smaller generic medicines companies, a major deterrent. For the larger companies it involves not only cost but lengthy use of legal resources that could be utilised elsewhere. Clearly, patents and intellectual property should be defended. However, the results of the Inquiry surely indicate that defence is often initiated from weak ground in many cases. The existence of a 'community' patent and a single European patent litigation system would go a long way to removing some of these commercially inspired defensive patent strategies. Whatever the consequences, the emphasis should now be on a quick implementation of the recommendations in order to bring transparency to what is often a delicate area for all concerned.

BIOEQUIVALENCE

Some originator companies continue to imply that generic medicines may be less safe and effective than the branded counterpart. This is considered to be an unfounded claim. Indeed, a recent review and meta-analysis looking at the clinical equivalence of generic and brand-name drugs used in cardiovascular disease showed no superiority of the originator medicine over the generic medicine[6]. In the absence of sound clinical data, the use of a 'fear factor' in misinforming the public by the originator company should be prevented.

PATENT LINKAGE

Delays to generic medicine entry are sometimes caused by regulations in certain countries with regard to pricing approval following marketing or price and reimbursement authorisation. Further delays may then be encountered whilst waiting for reimbursement status, as shown in Figure 8.

Interpretation of the regulations in some countries may even delay granting of the marketing authorisation through a mechanism known as 'patent linkage'. In Portugal there are currently 140[7] law suits before the administrative courts using a specific provision of the Portuguese constitution to delay entry.

Originators have alleged that granting a marketing authorisation constitutes a violation of their process and product patents. This is despite EU legislation which states that the granting of a marketing authorisation should be based solely on quality, safety and efficacy data and not on other criteria such as economic factors. The administrative courts have even ignored claims from the generic medicines companies that their products do not infringe the patents. They have recently suspended the granting of marketing authorisations and pricing and reimbursement approval for a wide range of key molecules including atorvastatin, clopidogrel, escitalopram and others. These actions deprive patients in Portugal access to affordable medicines and delay potential savings for the payers (Figure 9 overleaf).

The Transparency Directive 89/105/EEC lays down maximum time-limits of three or six months for pricing and reimbursement decisions. This does not preclude Member States from establishing quicker decision making procedures where deemed appropriate.

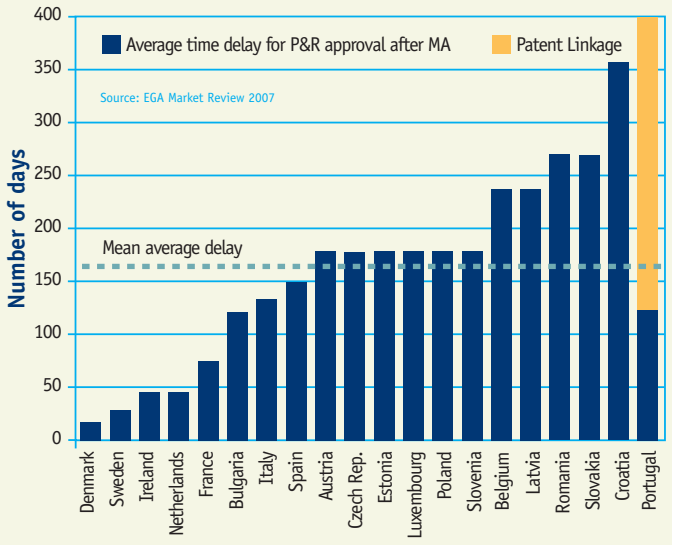
FIGURE 8. Time delays by country for price and reimbursement approval

COUNTRY	Austria	Belgium	Bulgaria	Croatia	Czech Rep.	Denmark	Estonia	France	Ireland	Italy	Latvia	Luxembourg	Netherlands	Poland	Portugal	Romania	Slovakia	Slovenia	Spain	Sweden	Total Yes	Total No	Total
Average Time Delay for Price Approval	180	90	90	180	90	14	90	75	45	135	120	30	N/A	180	21	90	120	15	75	30			
Average Time Delay for Reimbursement Approval	180	180	30	180	90	14	90	75	45	135	120	180	45	180	90	180	150	180	75	30			
Are the Applications for P&R of generic medicine's simultaneous?	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	No	No	No	Yes	No	Yes			
Average Time Delay for P&R Approval after MA	180	240	120	360	180	14	180	75	45	135	240	180	45	180	111	270	270	180	150	30			

Source: EGA Market Review 2007

[6] Clinical Equivalence of Generic and Brand-Name Drugs Used in Cardiovascular Disease: A Meta-Analysis. Kesselheim AS, Misono AS, Lee JL, et al. JAMA, 2008; 300(21):2514-26.
[7] Apogen, 7th December 2009

FIGURE 9. Time delay for price and reimbursement approval for a generic medicine after granting market authorisation.



Commenting on this issue, the EU Pharmaceutical Sector Inquiry recommended amendments to policies in those countries where delays have occurred. The Commission even went as far as to invite Member States to consider the granting of automatic/immediate pricing and reimbursement status to generic medicines where the corresponding originator product already benefitted from reimbursement based on a higher price. They concluded that this would considerably alleviate the administrative burden for all concerned and lead to faster access of generic medicines. This should happen sooner, not later.

The Inquiry was also critical of other delaying tactics such as 'settlement agreements' between originators and generic companies, abuses of a dominant market position and defensive patenting strategies.

THE GENERIC MEDICINES MARKET AND KEY DYNAMICS

The global pharmaceutical market is currently valued at US$720 billion, growing at 5% per year (MAT, March 2009). In Europe, the market is estimated at US$236 billion, growing at 5.8% per year, with a forecasted increase of a further US$45 billion in the time period 2008 to 2013.

Based on IMS MIDAS Market Segmentation data, the generic medicines market has an estimated value of €57 billion in the top 8 global markets with growth of around 8% in 2009, up from 3% in the prior twelve months. In Europe, the EGA estimate that the generic medicines market size is €31 billion and growing at rate of approximately 6% per annum. However, growth figures can be misleading for payers because they often overlook the fact that for each €1 increase in the value of the generic medicines sector, almost €3 on average are saved on total pharmaceutical expenditure. This reflects the lower price of the generic medicine used when compared to the price of the originator product, had this been prescribed. Thus, the higher the growth in the generic medicines market, the greater the savings that are made.

PRICING DYNAMICS

Pricing policies, reimbursement levels and generic medicines substitution are key dynamics in the generic medicines market. In some countries, such as Italy and France, the price of the generic medicine is directly linked to the price of the originator product whereas in other markets, such as the UK, there is relative freedom of pricing with competitive forces setting the price.

The pricing level in each country therefore varies considerably but generic medicines prices are always lower than the originator price, hence the potential for savings. While it is impossible to have one system throughout, for all the reasons we have mentioned, it is important to have coherent systems that create room for competition. The French system, for example, stimulates competition without destroying prices, thus delivering significant savings to the medicines bill yet maintaining adequate margins within the supply chain to provide the required service levels.

It should be noted, however, that if the price of generic medicines is very low, the incentive for pharmacists to dispense them is minimal since part of their remuneration is frequently based on the value of each item dispensed. Unless they are compensated for this loss in another way, pharmacists may not give full support to any generic medicines initiative. Noting the financial disincentives to dispense generic medicines that exist in many EU countries, Prof. Dr. Simoens in his paper goes on to show that where companies offer discounts to pharmacists, healthcare payers and patients do not capture the potential savings from generic medicines. Thus, price and reimbursement levels for generic medicines are important for all parties.

GENERIC SUBSTITUTION

Where patient co-payment policies are in place, generic medicines offer a lower financial burden for the patient but may be less attractive for the pharmacist to dispense. This depends on the regulations governing pharmacist reimbursement. For example, where the pharmacist receives a percentage of the price there is actually a negative incentive to dispense a generic as generics are always priced lower. This is where substitution rules may become important. Compulsory substitution for a prescribed originator medicine requires the pharmacist to dispense a generic medicine in order to be reimbursed. Optional substitution can be less effective as it allows the physician to specifically request that a particular product is not substituted. Some substitution rules include a price element whereby only generic medicines within a certain price band may be used as the substituted product.

The degree of generic medicine penetration and utilisation therefore also varies widely from country to country because of the local dynamics on the supply and demand side.

CHANGES IN PROCUREMENT

To date, the main focus around generic medicines has been on cost. Indeed, when governments see the growth in this sector they all too often assume that it is thriving and successful. In reality, many smaller generic medicine companies are struggling to stay in business; even the major ones deliver less than half the net income of the originator companies. Enforced price reductions, international reference pricing and procurement through tendering put the long-term future of the generic medicines industry at risk.

If 'tendering' is to remain then tenders for new generic molecules should only be considered after a period of time following launch, to enable a competitive position to be established. Generally speaking, tendering currently results in selection of the lowest priced product and for reasons explained earlier, supplies will then likely be sourced from manufacturers outside of the EU. Tendering currently predisposes to a monopoly supply position leaving exposure to all the threats and consequences associated with such a strategy.

Multi-sourcing of generic medicines within Europe is one of the competitive forces that ensure low prices, choice and continuity of supply. Complex logistics can further increase risks to continuity of supply especially if demand increases unexpectedly. Potentially a non-supply situation could arise if alternative sources of the product are no longer available in certain countries. Stock-outs with generics are inevitable at some point in time for a variety of reasons. Even if payers can contractually recoup costs from the manufacturer in the event of inability to supply, this may still lead to a patient being unable to access his usual medicine. Thus, tendering for generic medicines could in the long-term lead to an increase in costs as players withdraw from the market; indeed experience in the Netherlands has already seen manufacturers withdrawing certain molecules. Tendering also selects the lowest priced product on offer, ignoring all other attributes, which may be to the long-term detriment of the patient.

Tendering will certainly encourage consolidation which may or may not be in the interest of certain countries or players.

The 'Sunset' clause associated with market authorisations[7] could also lead to issues for manufacturers in the event of being unable to find a market for their products.

DISTRIBUTION

One key element in the market is the changing role of distributors in the generic medicine supply chain. Vertical integration (wholesaler acquisition of pharmacies) has seen wholesalers moving over time from logistics providers to customers. Some have even adopted their own private label supply of generic medicines. However, the major issue is the margin that generic medicines can offer to wholesalers and this has been exacerbated with the move by originator companies to a direct-to-pharmacy or customer approach. This has limited access to certain products for some wholesalers as well as squeezing margins, meaning that distribution costs for generic medicines as part of their overall business are causing financial issues. Where the fee for distribution is a fixed percentage of the medicine's price then the cost of distributing a product which cost just a few cents a pack is not financially viable. The challenge for distributors is compounded when you consider the extremely low prices resulting from tendering of generic medicines in some markets.

Proposals for a fee for each pack of generic medicines delivered have been suggested but, as already indicated, there is little margin within the price of a generic medicine to cover this additional cost in the absence of a price increase. This will only further discourage the supply of generic medicines in a market unless an equitable solution for both manufacturer and distributor can be found.

[8] EC 726/2004: Marketing authorisation lapses if the product is not placed on the market within three years of being granted authorisation or if it was previously on the market and has not been for a period of three consecutive years.

Rules and Incentives															
Market Rules	Mandatory price reduction	✓	✓					✓		✓	✓				✓	
	Patient co-pay		✓	✓			✓			✓	✓	✓	✓		✓	
	Price referencing			✓	✓	✓	✓		✓		✓	✓	✓	✓		
	Pharmacy-level substitution				✓	✓				✓	✓		✓	✓		✓
Market Incentives	At the pharmacy				✓	✓			✓	✓	✓		✓	✓		✓
	With the health insurers						✓			✓						
	With wholesalers										✓					
	With payers	✓	✓			✓										
	Favouring brands							✓				✓				
	Favouring generics	✓		✓			✓		✓		✓			✓	✓	✓

FIGURE 10. Differing rules & incentives for use of generic medicines across EU markets leads to different market forces.

MARKET RULES AND INCENTIVES

Market forces vary across the EU depending on whether the healthcare system in place focuses attention on physicians, pharmacists, wholesalers or payers (Figure 10).

Some degree of substitution, whether automatic or optional, exists in most EU countries which encourages generic medicine utilisation.

Only a few EU countries actively support the generic medicines industry publicly. Italy and Portugal are among the main proponents with public campaigns focused on increasing generic medicine consumption and changing physicians and pharmacists prescribing and dispensing habits, as well as increasing patient acceptance of and demand for generic medicines.

GENERIC MEDICINES: MARKET IMPACT

The generic medicines sector is dependent on a thriving R&D-based industry launching and developing a rich pipeline of innovative medicines.

With development costs for new medicines rising (particularly in the field of biotechnology), greater regulatory hurdles and tougher market conditions, fewer new products are being launched and those attaining 'blockbuster' sales of over US$1 billion are declining. The introduction of a generic medicine at the time of patent expiry puts further pressure on the R&D-based companies. Brand share erosion or switching to a generic medicine, generally now occurs quicker than ever before, with the UK and Germany being the fastest. However, in certain countries, such as Spain and Italy, erosion not only takes longer but also ensures that the level of switching is kept low (Figure 11).

Some R&D-based companies are finding it difficult to replace sales lost to generic medicines with sales generated from new products. This has led to many companies diversifying or consolidating while at the same time stimulating true innovation in the search for new medicines.

One thing is certain, in today's environment the R&D-based industry can no longer depend on the historical business models delivering the same levels of return.

FIGURE 11. Degree of generic erosion following loss of exclusivity.

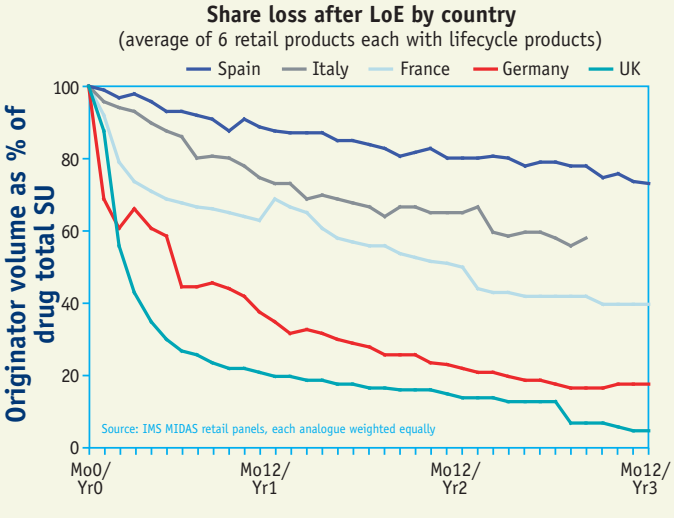


FIGURE 12. Medicines with a value of $137 billion are losing patent protection in 8 key markets (Canada, France, Germany, Japan, Italy, Spain, UK and US) through 2013.

Over the next five years, medicines with a value of over US$137 billion will lose protection in the eight major world markets, bringing further challenges to the R&D-based industry (Figure 12).

Utilisation of generic medicines in place of these patented medicines in the future offers a huge potential for savings.

With each new generic launched, additional pressure is brought to bear on originator products as Health Technology Assessments (HTAs) focus on cost of therapy. Their demands for ever increasing amounts of data on cost benefits leaves 'Me Too' products with little space in today's markets.

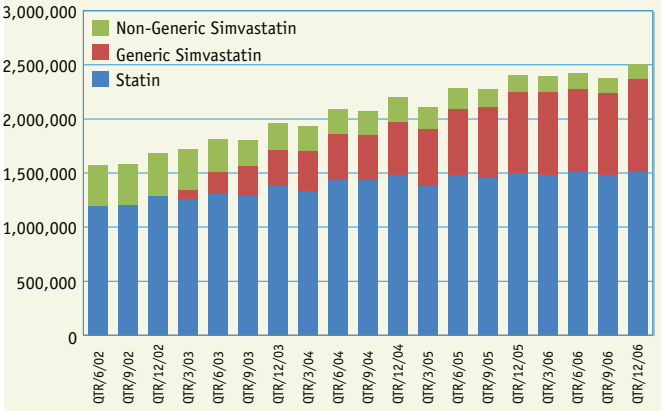
EXTENDING MARKET MONOPOLY BY LIFECYCLE STRATEGIES

The threat of significant revenue losses from patent expiries has led originators to develop enantiomers or different polymorphs or salts of blockbuster products in order to prolong the lifecycle of the brand.

Molecules such as omeprazole, citalopram and loratidine have been replaced by esomeprazole, escitalopram and desloratidine, respectively. Despite comments that they offer only limited advantages, if any, over the original medicine, in many instances, supported by large advertising and promotional expenditure, they have successfully switched physician prescribing from the original brand to the 'new' product. This has resulted in the loss of significant savings for payers and indeed continuing growth in expenditure for these molecules through the extended patent life of the new alternative.

[9] Generic Bulletin, 2008

FIGURE 13.
C10A Cholest&Trigly Regulator market - Volume.



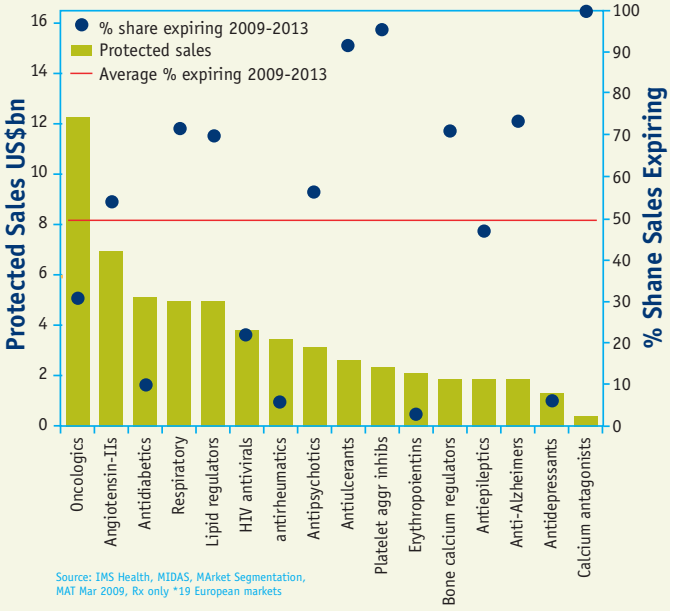
More recently, the pharmaceutical firm Servier was accused by the Danish generics industry (IGL) association of using the practice of evergreening in Denmark to extend the life-cycle of their product Coversyl©, an antihypertensive product, by introducing onto the market a "therapeutically identical" version of Coversyl©, called Coversyl Novum©. As reported in the industry press: "By promoting Coversyl Novum—which contains perindopril arginine rather than the original tertbutylamine salt—at different strengths to the original, Servier is attempting to protect its monopoly on the ACE-inhibitor...."

The costs of Coversyl Novum© to the Danish healthcare system in 2007 was €10.7 million. According to the IGL, the use of the generic formulation could potentially have saved the authorities €8.1 million.[9]

Generic entrants have the potential to impact a whole therapeutic category as evidenced when a gold standard therapy loses patent protection. The launch of a generic medicine version of the leading anti-ulcer drug omeprazole made the drug affordable for use in less serious conditions such as gastro-oesophageal reflux, in addition to the savings in ulcer therapy. A similar effect was shown when generic simvastatin entered the market. A lower, affordable price supported with positive clinical data expanded the statin therapy category, opening up lipid treatment for a whole new population of patients (figure 13).

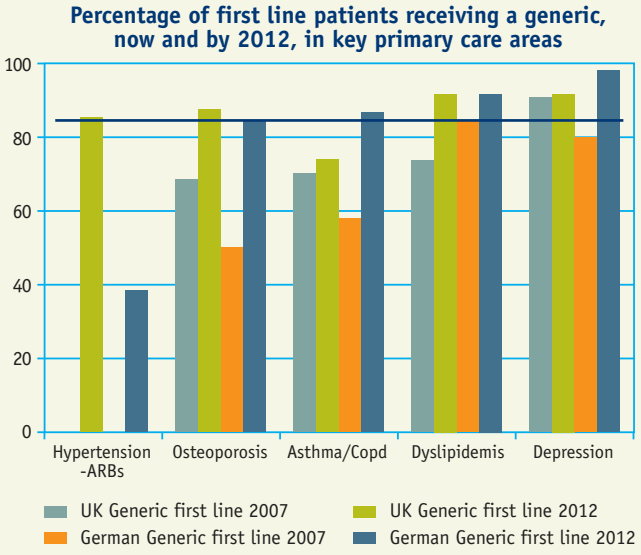
The potential for greater savings will continue as a range of products lose patent protection in many therapy areas over the next five years (Figure 14 overleaf). It is for this reason that most R&D-based companies are focused on delaying or preventing the entry of a generic medicine; as soon as it is launched the continuing existence of the brand is under threat.

FIGURE 14. Key therapy classes face significant generic exposure in Europe* in the next five years.



Source: IMS Health, MIDAS, MArket Segmentation, MAT Mar 2009, Rx only *19 European markets

FIGURE 15. Potential exists for Payers to recommend a generic medicine as first line therapy in key primary care areas.



Source: IMS Disease Analyser Germany, UK, 1st line use defined as new to pharmacotherapy – ARBs=Angiotensin II receptor antagonists (antihypertensive class)

Whatever it takes, the generic medicine industry should not be subject to unfair practices which either reflect abuse of a dominant position or disincentivise the use of generic medicines by R&D-based companies. This may be applicable if the originator companies find that the risk to their business of lost patent protection on major products over the next three years is sufficiently high to warrant new pricing strategies or changes to the way patients access these medicines.

OPPORTUNITIES ARISING FROM INCREASED USE OF GENERIC MEDICINES

DRIVING FIRST-LINE USE

One alternative to focusing on the price of generics could be a treatment regimen approach for some of the major indications where generic medicines represent the gold standard therapies. The opportunity to commence first-line therapy with a generic medicine exists in many of the most common disease areas (Figure 15).

This formulary-style approach would give confidence in using the appropriate medicine whilst at the same time providing a sound basis for calculating future costs of therapy in these selected areas. Competition between generic medicine manufacturers would still remain as they have duplicate product portfolios, and continuity of supply would not be an issue. Adequate reimbursement schemes could then be formulated for pharmacists to ensure profitability and confidence in dispensing generic medicines.

INCENTIVISING INNOVATION

The development expertise within the generic medicines industry is recognised as being innovative. Indeed, it is the level of skill in chemistry and process development that has driven the successful introduction of so many generic medicines. Furthermore, there is an understanding within the industry of patient and pharmacist needs in relation to patient-oriented packaging, arising from the production of a wide range of products across many countries. Certain generic medicine companies have produced packaging specifically designed to help patients and minimise pharmacy dispensing errors. Others have developed fixed combinations of routinely co-prescribed off-patent medicines such as diuretic/potassium conserving and non-steroidal/proton pump inhibitor combinations to aid patient compliance. If the pressure is only on costs without any incentive for advancements in this area then the potential will never be manifested.

Once an originator product loses exclusivity, most research is terminated; in fact it may cease well before this time as the period to recoup any additional research costs will be limited. Many older generic medicine molecules never maximised their therapeutic potential for this reason. In some instances, new indications or uses did appear but much later than might have been expected had the appropriate level of research continued. Unless rewarded, opportunities for further development will never be pursued and yet the benefits to patients could be significant.

ENCOURAGING INVESTMENT

The European generic medicines sector has to compete on a global scale, which includes competition from manufacturers with facilities outside of Europe. Lack of flexibility in regulatory procedures and financial incentives has sent European-based pharmaceutical development and manufacturing into a decline. Although a positive move, the Bolar provision does not go far enough to level the playing field for European-based generic medicines manufacturers.

The existence of grants and low interest loans for building production facilities and export incentives with tax breaks in non-European countries produces cost advantages which cannot be obtained within the EU.

The opportunity exists for governments and payers to incentivise the European generics medicine sector in order to generate a sustainable generics medicine industry which can deliver cost savings through good patient management with gold standard therapies at affordable prices.

CONCLUSIONS

The generic medicines industry is now an essential and integral part of healthcare delivery across Europe, supplying over half the volume demand for medicines but representing less than 18% in cost terms. Its contribution to savings in pharmaceutical expenditure and broader access to medicines has secured the provision of quality healthcare across the region. Without the presence and availability of affordable generic medicines it is doubtful whether governments and payers could have sustained the growing demand for medicines.

The potential savings in the major markets from utilisation of generic medicines in place of those originator brands losing exclusivity over the next four years is projected at around US$100 billion, the highest ever level. Beyond this period, the number and nature of opportunities for savings diminishes as products from biotechnology replace small molecule medicines. With generic medicines unable to compensate for the growth arising from innovative products, pharmaceutical expenditure will escalate.

The savings arising in the next four years should be used to formulate a longer- term plan for the utilisation of generic medicines.

The gold standards of many therapies in the treatment of cardiovascular disease, CNS disorders, GI problems and many other chronic ailments are available now (and certainly will be in the near future) as generic medicines. Initiation and continuation of therapy through treatment schedules in these disease areas should involve the use of a generic medicine as first-line therapy. This would generate sustainable savings allowing for the use of truly innovative medicines in those diseases requiring such therapy.

Attempts to control medicine expenditure using price as the sole parameter not only puts the generics industry at risk but also all the players involved in healthcare delivery, including pharmacists and distributors. Enforced and unpredicted price cuts cause serious damage across the industry, having a destabilising effect and making planning impossible. This will be to the detriment of any healthcare system in the longer-term.

The varied nature of healthcare systems within Europe means that what is successful in one country may not be applicable in another. Importing one aspect of healthcare from another country could have major consequences.

The generic medicines industry is perceived as a threat to the R&D-based sector. However, recent examples of diversity witnessed within originator companies reflect the changing dynamics and will lead to increased competition across all markets. This should be to the benefit of healthcare providers and ensure sustainable business models for the pharmaceutical industry.

What should not be allowed to happen is any abuse of a dominant position by the R&D-based companies that leads to unfair competition or use of delaying tactics that cannot be defended. Swift implementation of the EU Pharmaceutical Sector Inquiry recommendations will be essential to removing hurdles to the timely introduction of new generic medicines, specifically in the area of pricing and re-imbursement.

Sustainability of the generic medicines industry is one of the key elements in ensuring the continuity of broad access to medicines. To meet the rising demand from more patients who are living longer lives, requiring chronic therapy and expecting an improved quality of life, generic medicines offer established treatment at an affordable price. There is no other single, simple solution.

KEY TAKEAWAYS

GENERIC MEDICINES:

- Provide an affordable, gold standard medication for many major illnesses
- Allow access to medicines for a greater proportion of the population
- Stimulate healthy competition with the branded sector
- Deliver savings to national health bills
- Enable future long-term savings in the expanding role of medicines vs hospitalisation
- Are high quality products

IMS Health and the EGA have worked closely and collaboratively over a number of years on issues relating to the generic medicine industry.

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IMS HEALTH

Operating in more than 100 countries, IMS Health is the world's leading provider of market intelligence to the pharmaceutical and healthcare industries. With US$2.3 billion in 2008 revenue and more than 50 years of industry experience, IMS offers leading-edge market intelligence products and services that are integral to clients' day-to-day operations, including product and portfolio management capabilities; commercial effectiveness innovations; managed care and consumer health offerings; and consulting and services solutions that improve productivity and the delivery of quality healthcare worldwide. Additional information is available at http://www.imshealth.com

EGA

The EGA is the official representative body of the European Generic medicines and Biosimilar medicines pharmaceutical industry, which is at the forefront of providing high-quality affordable medicines to millions of Europeans and stimulating competitiveness and innovation in the pharmaceutical sector.

Formed in 1993, the EGA represents generic pharmaceuticals companies and their subsidiaries from throughout Europe, either directly or through national associations. Companies represented within the EGA provide approximately 150,000 jobs in Europe. Cost-effective generic medicines save EU patients and healthcare systems over €30 billion each year, thus helping to ensure patient access to essential medicines and providing urgently needed budget headroom for the purchase of new and innovative treatments.

The EGA plays an important consultative role in European healthcare policy-making. The EGA and its members work with the European national governments and the EU institutions to develop affordable solutions for pharmaceutical care and to increase Europe's competitive strength in the global pharmaceutical medicines market.

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