

Falconbury

The Pharma BusinessMAsters™

Module 1

Introduction to Pharma

John Ansell

John Ansell is a biochemistry graduate with a Masters degree in Business Studies. John began his 20-year career in international marketing and business development in Holland with Organon, worked for Schering AG and Fisons in the UK, and again in Holland, with Solvay. Finally, from 1985 to 1989 he worked at Glaxo Holdings, on Zantac. Subsequently, as an independent industry consultant, John has worked for over 100 clients on commercial strategic projects. He is a frequent speaker, and has also acted as chairman of over 30 industry conferences. John is the author of more than 40 articles and reports on strategic industry issues.

Course helpline:

Tel: +44(0)20 7729 6677

Email: distancelearning@falconbury.co.uk



Falconbury Ltd
10-12 Rivington Street
London EC2A 3DU

Telephone: +44 (0)20 7729 6677

Fax: +44 (0)20 7729 6110

Email: distancelearning@falconbury.co.uk

Web: www.falconbury.co.uk/distancelearning

© In this format Falconbury, produced under licence by
permission of Thorogood Publishing Ltd 2008

All rights reserved. No part of this course may be reproduced,
stored in a retrieval system or transmitted in any form or by any
means, electronic, photocopying, recording or otherwise, without
the prior permission of the publisher.

This course is sold subject to the condition that neither it nor the
Modules that it comprises of, be lent, re-sold, hired out or
otherwise circulated without the publisher's prior consent in any
form of binding or cover other than in which it is published and
without a similar condition including this condition being
imposed upon the subsequent purchaser.

No responsibility for loss occasioned to any person acting or
refraining from action as a result of any material in this course
can be accepted by the author or publisher.

INTRODUCTION TO PHARMA

CONTENTS OF MODULE

1. WHY A PHARMA 'BUSINESS MASTERS'?	5
Emphasis on practice in the pharmaceutical industry	5
What is distinctive about the pharmaceutical industry?	5
Drug discovery and development	9
Original brands and generics	13
Market dynamics and external pressures	22
The international dimension in pharmaceuticals	25
US versus Europe	27
Emerging markets	33
The need for specific techniques for pharmaceuticals	37
2. SELF-ASSESSMENT QUESTIONS FOR MODULE 1	38
Your next Module will be:	39

1. WHY A PHARMA 'BUSINESS MASTERS'?

The impact of major patent expiries, the growth in strategic alliances and partnerships, the drug development crisis, slowing industry growth and consolidation are just a few of the issues currently confronting top pharma management. One key question facing these executives is whether, within their organisations, the skill set exists which is needed to drive the business forward in this tough environment.

In order to succeed it is vital that as an individual working within the pharma sector you should develop not only the expert technical skills required, but also the key business and management skills needed to ensure that your company can take a dynamic approach to overcoming each challenge.

This distance learning programme offers the unique opportunity to develop your key skills as a high performance business leader within the pharmaceutical sector at your own pace, and in your own space without the additional costs of travel and time away from work.

Emphasis on practice in the pharmaceutical industry

This course will concentrate on management techniques in practice in the pharmaceutical industry. Whilst it will also refer to some of the other most important concepts in general management strategy, this will not be the focus of the course. The reason for this is that there is a limit to the applicability of standard management techniques to any particular industry. This is particularly the case with the pharmaceutical industry.

Experience has shown us that training participants are much more interested in the material relating directly to practice in the pharmaceutical industry than they are to standard management techniques content. This has therefore, governed the emphasis which we have given to the material in this course.

What is distinctive about the pharmaceutical industry?

The pharmaceutical industry is distinctive in a number of ways from other industries. It is important to get to grips with these.

Who is the customer?

Although the patient consumes medicines, it is the doctor who prescribes them. This immediately introduces a disconnect between the (physical) consumer and the prescriber/immediate decision-maker. It also means that the primary, although not the only, target for pharmaceutical marketing is the doctor. Each doctor is primarily responsible for the prescribing of a very considerable quantity of often expensive pharmaceuticals each year.

Because the number of doctors in the general population is relatively limited, it is cost effective for pharmaceutical companies to promote their products very actively through salesforces and other promotional media targeted at doctors. We deal with marketing in Modules 8-10, and the topic of product promotion specifically in Module 10.

Regulation

Since the 1960s pharmaceuticals has become a highly regulated industry. Drugs have to be shown to be safe and effective. Increasingly nowadays they also have to be shown to be cost-effective. Not only does this mean that it normally takes many years to satisfy the regulatory authorities of the suitability of a new product for approval. It also means that there are also strict constraints on how an approved product may then be marketed.

Intellectual property protection

The key type of intellectual property protection universally for pharmaceuticals is patent cover. And unlike with consumer products, copyright is not often of great consequence in pharmaceuticals.

The standard patent term from filing is 20 years, though various forms of extension are available. Once all intellectual property protection has expired, then to most intents and purposes the life of the product as a marketed brand has passed. This is quite different from other industries, where brands can often be maintained over very many years.

Costs and timescales

Let's look at *timescales* first. Firstly, let's consider R & D. The figure below shows that on average a new product takes 10-12 years to develop. We will discuss the whole process in the section of this Module on Drug discovery and development below.

Discovery/ Preclinical Testing		Clinical Trials			FDA		Phase IV
Years	6.5	Phase I	Phase II	Phase III	1.5	15 Total	
Test Population	Laboratory and animal studies	20 to 100 healthy volunteers	100 to 500 patient volunteers	1,000 to 5,000 patient volunteers	Review process/ approval		Additional post- marketing testing required by FDA
Purpose	Assess safety, biological activity and formulations	Determine safety and dosage	Evaluate effectiveness, look for side effects	Confirm effectiveness, monitor adverse reactions from long-term use			
Success Rate	5,000 compounds evaluated	5 enter trials			1 approved		

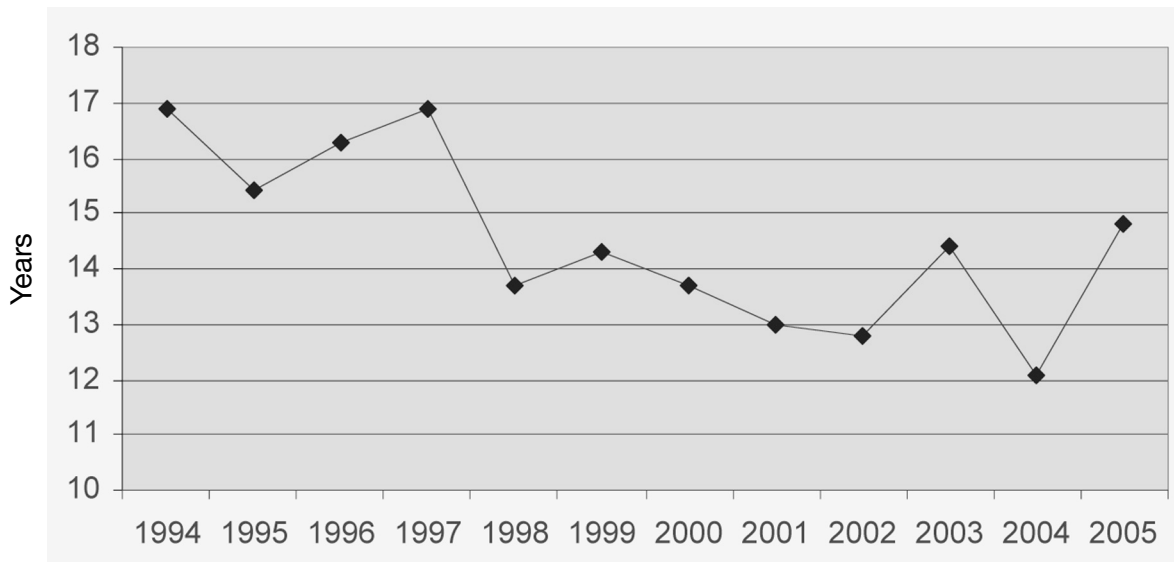
Source: Kelly, PhRMA web site

Figure: The Drug Development and Approval Process

The consequence of such a long development process for new products is that R & D costs are very high for pharmaceuticals in comparison with other industries' products.

Since the patent term for a pharmaceutical compound begins to run when the patent is filed, it might seem that not much time remains after a new product is launched before its patent expires. But, in reality, because subsequent patents of value can often be filed, and other types of intellectual property protection can apply, it means that on average global sales for a product only peak after it has been on the market for about 13 years. (We deal with intellectual property protection in a separate section below in this Module – Original brands and generics: types of intellectual property protection.)

Sales of the majority of products thereafter normally decline quite sharply as generic competitors erode their sales, so that effectively the active life of the original brand is over.



Source: John Ansell Consultancy

Figure: Average global longevity

This time to peak sales, termed longevity, has been stabilizing at around 13 years over the past few years.

Therefore, the life of a pharmaceutical product is in total about 25 years. It divides neatly into two roughly equal halves: the first half is taken up with developing the product to the point of regulatory approval and the second half is devoted to marketing it.

When we examine the *cost structure* for pharmaceuticals it is quite different from that of other industries. It is shown in the figure below:

R & D	16.5%
Cost of goods	13.2%
Sales & marketing	35.0%
General & administrative	8.0%
Total	72.7%
Margin	27.3%

Source: PharmaStrategy

Figure: Pharmaceutical cost structure (as percentage of sales)

R & D costs

R & D accounts on average for the equivalent of 16.5% of sales turnover. It reflects the long duration of the R & D process and the complex and demanding nature of regulatory requirements. 16.5% is the highest percentage for any industry, and very much higher than for most others; only a handful spend over 6% of their sales on R & D.

Manufacturing costs

Pharmaceutical manufacturing is not labour intensive as in many other industries and so manufacturing costs are typically only 10-15% of sales. For new products the figure is often well under 10%.

Sales and marketing costs

Across industries, marketing costs typically amount to 35-40% of a product's selling price. The figure of 35% for pharmaceuticals is very much in line with this.

Net margin

With general and administrative costs accounting for a further 8%, this means that net margins in the pharmaceutical industry are typically 25-30%. This is higher than for most other industries. But pharmaceuticals is also a relatively high risk industry: high risks and high gains apply.

What counts most in pharmaceuticals?

The consequence is that, crudely, pharmaceutical success is much more about maximising revenue than reducing costs – because in pharmaceuticals the scope for the former is much greater than for the latter. For example, curbing manufacturing costs are an issue for most industries. But in pharmaceuticals they will not make or break the company – whereas how successful a newly launched product will be could do so.

Maximising revenue means above all that pharmaceutical companies must ensure that they have sufficient new products to survive and prosper – they are the lifeblood of the industry. Pharmaceutical companies therefore put immense efforts into developing new products through their own pipelines. And all today augment this through licensing: acquiring rights to products either already on the market or in development by third parties. For if they fail and patents run out on their existing products, there would be no future for the company.

Drug discovery and development

As mentioned above, it takes approximately 10-12 years to develop a new chemical entity into a marketable product.

The first step in producing a new pharmaceutical product is to identify a specific target – for example, a molecule that plays a crucial role in a particular disease. Chemists, pharmacologists and biologists then screen thousands of compounds – or chemically or genetically engineer new ones – to generate lead compounds. These have some desirable properties, but usually have to be modified to increase their activity or minimise side-effects. This process is called *lead optimization*. It produces hundreds of potential drug candidates.

Criteria for selecting compounds for further testing researchers are:

- Is it likely to prove more effective than current therapies?
- Will it be possible to manufacture it – and at a realistic price?
- Will it be likely to have a reasonable dose range?
- Is there a presentation that can deliver it? For example, tablet, inhaler or injection?

Any of the above criteria can be critical to future development. It may not be possible, for example, to manufacture the drug safely, or to proper specifications, or at an acceptable price.

Pre-clinical testing

Once a drug candidate has been identified in the laboratory, pre-clinical development begins. Laboratory and animal studies then evaluate its safety and demonstrate that it has biological activity against the disease target.

Key pre-clinical tests include *pharmacokinetics*, i.e. how a drug moves through a living organism. Four key processes are involved:

- absorption
- distribution
- metabolism
- excretion.

This battery of testing ensures that the compound reaches its intended target and passes through the body properly.

In addition to such tests, a number of other pre-clinical studies are necessary:

- Chemistry tests to establish a compound's purity, stability and shelf-life.
- Manufacturing scale-up work to determine what will be involved in producing the medicine on a large scale.
- Pharmaceutical development involves dosing, packaging and formulation work (e.g., tablet, inhaler or injection).

The main goal of pre-clinical studies is to rigorously assess safety before testing in humans can begin. This can take anything between three and six years. Some pre-clinical safety tests continue even after the clinical trials have begun. These aim to determine whether there are any long-term adverse effects.

After pre-clinical testing is completed, in the US the next step is to file an Investigative New Drug (IND) application with the Food and Drug Administration (FDA) prior to beginning any human testing. This application must contain:

- results of pre-clinical work
- the chemical structure of the compound
- its presumed mode of action
- any side-effects found in animal studies
- how the compound is manufactured.

Other regulatory authorities have less demanding requirements at this stage, or none at all.

The IND must also include a detailed clinical trial plan, including how, where and by whom the studies will be conducted.

Clinical trials

These determine whether the drug is safe and effective in man for the disease in question. Only about 2% of compounds entering pre-clinical testing will succeed in reaching clinical trials.

There are three phases of clinical trials:

- *Phase I:* The compound is tested in a small group (typically 20-100) healthy volunteers, often in a hospital setting, to determine its safety profile, including the safe dose range. Pharmacokinetic studies in man examine how a compound is absorbed, distributed, metabolised and excreted, as well as the duration of its action. Phase I studies typically take 6-12 months to complete.

- *Phase II:* In this phase, placebo-controlled trials involving approximately 100-500 patients with active disease are set up. The goal of this phase is to establish proof of concept – i.e. that the compound is effective in treating the disease. Researchers also continue during this phase to:
 - evaluate the compound's safety
 - monitor for side-effects
 - determine the optimal dosage strengths and schedule (e.g., once or twice daily).

Phase II studies also tend to take 6-12 months to complete, though on average take slightly less time than Phase I does.

- *Phase III:* The compound is tested in large, randomized, placebo-controlled trials with much larger numbers of patient volunteers – between 1,000 and 5,000 – to generate statistically significant data. Patients are closely monitored at regular intervals to confirm (or not) that the drug is effective and to identify side-effects. Phase III studies can take 1-4 four years to complete, depending on the nature of the disease, length of the study, and the number of patients required.

Whilst Phase I-III studies are taking place, a number of crucial studies are conducted in parallel:

- toxicity tests and other long-term safety evaluations
- further development of dosage forms
- continued scaling up of production
- pack design
- preparation of a regulatory dossier.

Regulatory submission

When all three phases of the clinical trials are complete, all data reported in trials is analysed. If the company considers that the findings demonstrate that the experimental medicine is both safe and effective, the company can then file its regulatory dossiers.

The two major regulatory bodies now are the Committee for Medicinal Products for Human Use (CHMP) for Europe, and the FDA for the US. For the latter the regulatory dossier which has to be submitted at this stage is a New Drug Application (NDA).

Regulatory dossiers typically run to 100,000 pages or more. They must contain information on all studies conducted – including pre-clinical testing, all clinical trials, dosing information, manufacturing details and proposed data sheet information or labelling (the latter being the US term) for the new medicine.

Regulatory approval

In this final stage, the regulatory authorities review results from all the studies carried out over the years and decide whether they convincingly show that the product is sufficiently safe and effective to be allowed onto the market.

In the US, depending on the product and disease in question, the FDA commonly convenes an Advisory Committee meeting. Here, independent panels of experts appointed by the FDA consider data presented

by company representatives and FDA reviewers. Committees then vote on whether the FDA should approve an application, and under what conditions. It can:

- recommend a product for approval
- conclude that a product is non-approvable
- conclude that a product is approvable. This term is ambiguous but means the committee has decided that, with that further work (e.g. additional clinical trials) the product could then stand to be approved.

The FDA is not required to follow the recommendations of the advisory committees, but they normally do so.

Once the product is approved, doctors may prescribe it, it may be distributed to the pipeline and be marketed by the pharmaceutical company in question to doctors.

In 2003, the average approval time was 17 months for those products actually approved. The proportion of rejected applications in the US has for some years been about 10-15%. In recent years, the proportion of products deemed by Advisory Committees to be 'approvable', i.e. not immediately marketable, has been rising.

To this point, the time taken to develop a new product is typically 10-12 years. The cost usually quoted to achieve this is commonly quoted as \$800 million, though this figure is out of date – the real figure is probably about double this today.

Phase IV

Even after approval, studies and observations continue. The number of patients who will begin to use a product after its approval is usually vast compared with the thousands of patients who have already received it in clinical trials. With this larger scale of usage, rare side-effects may occur, and so companies must continue to monitor a new product carefully. Major regulatory authorities require manufacturers to continue to submit periodic reports, including on any adverse events.

Sometimes additional studies are required. Known as Phase IV or post-marketing studies, they evaluate long-term safety or generate more data on how the product affects a particular group of patients (e.g., children or the elderly). Phase IV studies can continue for years. For a successful product their cost can eventually vastly outweigh the clinical costs of getting the product onto the market.

Depending on the findings, a company can use the studies to submit further data – in the US in a *Supplemental NDA* – to seek additional indications for the product. These are becoming more frequently submitted by pharmaceutical companies, because the scope for new indications and presentations is being more actively capitalised upon by them (see also Module 10).

Original brands and generics

Types of intellectual property protection

Of the several types of intellectual property protection that exist, three are of particular importance in pharmaceuticals:

- *Patent cover:* Various types of patents are filed from the time when a new compound is discovered. Firstly, patents on the compound are filed. These usually provide the strongest type of patent cover. In due course process patents are normally filed. And whenever a product or process are modified, there may be potential for further patents to be filed.

Patents provide various strengths of protection. 20 years is the norm for a compound – and hence original brand – but each country has its own system. Types of patents that have proved powerful in extending intellectual property protection include those applying to devices used to deliver products – for example, inhalers for asthma products such as Ventolin (salbutamol, GlaxoSmithKline) onwards.

The strength of patents on a specific product are often highly unpredictable. It can be the case that only just before all patent cover expires the situation is still unclear.

Restoration of patent time can also be granted to compensate a company for delay in registering a product.

- *Market exclusivity:* This form of intellectual property is also very important, particularly in the United States, where the marketing exclusivity period starts from the date of launch. This protection applies irrespective of patent status. The FDA, which is responsible for regulating pharmaceuticals, defines marketing exclusivity as:

“a period of time during which others may not obtain approval for a generic copy of the listed new drug product for a use(s) for which exclusivity was granted.”

Marketing exclusivity has been in force in the US since 1984. This period was 10 years for products approved by the FDA between 1982 and 1984. Calculations for subsequent years are not straightforward but have in practice turned out to be at least 5-7 years. Some types of products, notably antibiotics, are not covered.

- *Trademark:* Trademark design protection can also apply, particularly to devices. For example, design protection for inhalers to deliver respiratory drugs can provide additional protection.

These forms of intellectual property generally allow a long duration of intellectual property protection. In practice they provide well over 20 years of cover on average from the date of first patent filing. This offsets the fact that development time in pharmaceuticals takes up 1-12 years on average after patents are first filed. This is superior to intellectual property cover in many other industries.

Because intellectual property protection is generally of longer duration in the United States, it has become the norm for:

- the period from launch to exhaustion of all effective intellectual property rights to be longer than in the US than other countries, notably in Europe.
- entry of generic and erosion of sales of original brands to occur later in the US than in Europe.

More sustained and powerful intellectual property protection has been an important factor contributing to the greater commercial value of products in the US than elsewhere. (See also later in this Module.)

Generics

When a drug's patent expires in a given country and all other types of intellectual property protection have expired, generic versions are allowed to enter that market. Since these are launched at a discount to the original brand, price competition is created. Where there are just one or two competitors, price erosion may not be major – typically 20%. But as soon as more generic competitors enter the market, more intensive price competition will soon ensue.

The prices of original brands have tended to rise internationally in real terms over the past 50 years. In turn, the **sales** of leading branded products have tended to rise considerably in real terms over this time. This has tended to attract into the market increasing numbers of generic players. Hence generic competitors, when they enter the market, have grown more fierce. Generic erosion has consequently occurred more quickly and prices have dropped to lower levels faster than would formerly have been the case.

The US is the biggest and most competitive pharmaceutical market of all. Branded drug prices tend to be higher there than elsewhere and therefore, generic prices usually have farther to fall there than elsewhere (see also below and in Module 9, Pricing). Consequently it has become common in the US for price erosion for major products to be 80% within a year of patent expiry – and recently, sometimes much more quickly than this.

Historical development of generics

In the early 20th century, generics were the main form in which drugs were prescribed (Redwood, H., *The Pharmaceutical Industry – Trends, Problems and Achievements*, 1987). In the US this had declined by 1948 to 40% of all prescriptions. By 1965 the generics share had fallen to 5% as newer, branded drugs took over the market.

It was only from 1984, with the passing of *Waxman-Hatch* legislation, that Abbreviated New Drug Applications became possible, easing the way for the approval of generics in the USA. This legislation was a trade-off: in return for easing the path for generic approval, a period of marketing exclusivity (as described above) was granted for new products.

The table below shows the considerable variation in market penetration by generics in Europe. By volume there is an eight-fold difference between Italy, with 6% market penetration, and the Netherlands, with half of its total sales volume as generics.

In value terms there is also an eight-fold difference between Italy, with 2% market penetration, and the Netherlands with 17%. As the table shows, there is much higher penetration in Northern European countries than in the rest of Europe. One factor responsible for this is that prices tend to be higher in Northern Europe.

Outside Europe, generic penetration by value is high in North America: 17% in Canada and 12% in the USA, but low in Japan: just 2% by value (2004 data).

Market shares for generics in selected European countries in 2006

	By volume	By value
Netherlands	50	20
UK	65	25
Germany	57	20
France	17	10
Belgium	13	10
Spain	12	6
Switzerland	10	3
Italy	7	3

Data extracted from European Generic Medicines Association (EGA) website, based on IMS data (3/07)

Though in the US the Waxman-Hatch legislation introduced a marketing exclusivity period for new drugs, by the end of the 1980s the revival in generics there was beginning to gather pace. This was stimulated also by the need for the government to curb swiftly rising healthcare expenditure.

In the other sizeable countries with free pricing, Germany and the UK, similar advances in generic penetration were also soon seen. However, in markets where drug prices were controlled (and therefore at a lower level than elsewhere), the attractiveness to generic companies, and their consequent penetration of the market, were correspondingly less.

Over the past decade, with continuing healthcare budgetary pressures, generic penetration has continued to rise in all countries. With governmental measures to encourage the use of generics, formerly low-penetration markets like France, Spain and Italy have (in that order) begun to change. The Table below shows that penetrations by value over the past 20 years have more than doubled in all of these countries, and with the striking exception of the even stronger growth in the UK, to a relatively uniform degree.

**Market share trends by value in selected countries over two decades
(% penetrations)**

	1984	2006
Netherlands	8	20
UK	5-6	25
Germany	8	20
France	2-3	10
Canada	6	17
USA	3	20

Source: John Ansell Consultancy, based, for 1984, on author's estimates in Redwood, H., *The Pharmaceutical Industry – Trends, Problems and Achievements*, p. 236, 1987) (except for US: IMS), and EGA and IMS data for 2004-06

Progress of generics by country

Northern Europe

Germany

Germany was one of the first major markets in the second half of the 20th century where generic penetration advanced. It is still amongst the leaders. The government and sick funds (Krankenkassen) energetically encourage cost-effective prescribing. This is backed by doctor profiling, in which the doctors' prescribing behaviour is monitored.

As generic **prescribing**, i.e. without brand name, is not permitted in Germany, all copy products have to be branded, at least with the company name. As mentioned above, in contrast with most countries, Germany has always allowed free pricing. This encouraged the setting up of generic companies selling at a price below the level of the original branded product but at a sufficient level to cover the cost of promoting generics brands to doctors.

By 2005 the largest German generics company, STADA, was ranked No. 47 in the Top 100 global pharmaceutical companies by sales (*The Scrip 100*, pp 8 & 9, *Informa Healthcare*, 2008). Like other major German generics companies, Stada until recently ran a sizeable salesforce. But because of radical changes in the healthcare reimbursement system, this has now been discontinued and efforts are, according to the company, being switched to negotiating of key accounts.

Generics have not necessarily benefited from the introduction of reference pricing in Germany as had been expected (see also Module 9). Instead of replacement of original brands by cheaper generics, the originators often bring their prices down to the reference price level and sometimes succeed by doing so in maintaining volume penetration of the market. This has also happened in other countries where reference price systems have been introduced.

The Netherlands

The conditions in the Netherlands are in several respects similar to those in Germany. However, here as in most countries, generic prescribing (rather than by brand name only) is allowed. This – as the case in most other countries – encouraged the growth of unbranded rather than branded generics, without the need for them to be promoted as in Germany.

UK

Historically generics have been favoured in the UK. Doctor training encourages generic prescribing. There was a breakthrough for generics in 1985, when blacklisting was introduced (see Module 9), which removed listed brands in certain therapeutic categories from reimbursement by the National Health Service (NHS). These were largely genericised, or 'low-tech' areas of medicine. Up until then, the NHS had not specifically favoured generics, though doctors had been encouraged to prescribe cheaper versions of multi-source drugs, and there was a profit advantage, too, for pharmacists in dispensing generically.

There were several moves by UK governments after 1985 to apply the black list to a much wider range of therapeutic areas, like oral contraceptives, but radical additions have not been made. The UK has a relatively strong pharmaceutical industry and a positive trade balance in pharmaceuticals, and this no doubt played its part in dissuading the introduction of such measures.

An attempt by Glaxo to introduce branded generics – as in Germany – in the mid-1980s quickly failed. Pharmacists balked at stocking multiple brands for the same compound.

Originally there was higher generic penetration in hospitals than with GPs but over the past decade it has increased quite rapidly in the GP sector as well, with strong budgetary encouragement for GPs to prescribe generically. Computer prescribing has, as elsewhere, also encouraged generic prescribing by all types of doctor.

Southern Europe

In Southern Europe (i.e. the area encompassing the Latin language-speaking European countries), generic penetration has been slow to grow. These countries had in common firstly, that prices of branded pharmaceuticals tend to be pegged at lower levels by governments than is the case in Northern Europe, thus allowing less scope for generics to undercut them.

Secondly, though governments have often been in favour of generics, they failed to facilitate greater use by not removing impediments to their growth. For example, pharmacists need to be incentivised to dispense generics rather than branded products. If they receive simply a fixed percentage of a product's price, then it will be counterproductive for them to substitute generics for original brands.

Both stick and carrot encouragement usually needs to be applied to persuade doctors to prescribe generics rather than branded products.

As far as the major Southern European countries are concerned, over the past decade there has been increasing government encouragement of generics in France, Spain and Italy: generics are growing in importance in that country order. France shows the most marked growth in generic penetration in recent years. But even there, some impediments to generics still exist.

In Spain this is much more the case. For example, for pharmacists dispensing generics the cheaper the generic is the less margin they make. Consequently, Spanish pharmacists favour dispensing the most expensive generic available!

Italy is by far the least prepared of these three Southern European countries in enabling the growth of generics and has made the least progress to date.

This goes to show that even when countries wish to encourage cost-saving through greater generics use – as nearly all apparently do – unless a series of measures are in place to facilitate this, generics will not grow.

USA

In the USA, as is often the case elsewhere, not all generic prescriptions are dispensed generically. Some revert to branded products depending on the decision of the pharmacist. On the other hand, generic substitution of branded prescriptions also occurs.

Prior to the 1984 Waxman-Hatch legislation, mentioned above, came into force in 1984, with free pricing, conditions were still sufficiently favourable for generics to increase their volume penetration steadily, from 9% of prescriptions written in 1974 to about 19% in 1984. The Waxman-Hatch legislation enabled the simplified registration of generics via the introduction of Abbreviated New Drug Applications (ANDAs), a cut-back version of the NDA needed to register a new chemical entity.

But, offsetting this, particularly for the first few years after it was enacted, was that this legislation for the first time granted several years of market exclusivity for a new chemical entity after it had reached the market. This meant that generics only began to benefit from the legislation towards the end of the 1980s when more plentiful new generic opportunities began to arise with the expiry of the quite extensive marketing exclusivity periods the 1984 legislation had allowed.

A further factor driving up generic use at that time was the competitive provision of drug benefits in public and private sector health plans. Along with more traditional types of health insurance institutions, managed care systems such as health maintenance organisations (HMOs) began to grow. These appealed particularly to companies running corporate health plans. Such managed care systems which had offered drug benefits were found to help in membership drives. However, it also put a strain upon their budgets.

But the net effect was a rise from the 1980s onwards in the proportion of US drug expenditure covered by public or private sector benefit plans, and growing pressures to curb the rising cost of drug benefits, particularly by means of generics.

At the same time this trend was reinforced at pharmacist level by the rise of buying groups and larger Preferred Provider Organisations (PPOs) whose rationale was to make drug purchases cooperatively on behalf of large numbers of independent pharmacies. And to reduce costs, bulk buying and use of generics was favoured.

From the late 1990s the growth of generics gathered pace, so that by 2006 63% of all prescriptions were dispensed generically, in which year they accounted for 25% of total US pharmaceutical sales by value. In 2006 US generics sales grew by 22% (all figures IMS data, as reported on the US Generic Pharmaceutical Association [GPhA] website). By that year generics accounted for 62% of all prescriptions and 20% of total sales (IMS data).

Authorised generics are a recent and controversial phenomenon in the US market. These are generics marketed under license from the patent holder. An example is Merck & Co's Zocor (simvastatin). This product lost its US patent protection in June 2006. The Indian generics company Dr Reddy made an exclusive agreement with Merck & Co by which it was allowed to market an authorized generic form of simvastatin under license from Merck. This prevented other approved generics from gaining early entry to the market and much reduced the size and attractiveness of the commercial opportunity open to them with this product. This in consequence helped to prolong the return that Merck & Co could obtain from simvastatin.

Japan

As with Southern Europe, Japan is another example of a country where the government emphasis has been on pegging and then reducing prices of original brands rather than on promoting generics.

Consequently the generics sector is small, though increasing. According to Social Survey Research Information (SSRI) in 2006, around 16% of the total Japanese market by volume and only 5% by value is accounted for by generics. However, 40% of Japanese doctors either already prescribe generics or are willing to allow brand-to-generic switching.

But so far there has been no great upward trend in Japan of the type seen elsewhere. This is principally because the government has failed to introduce the facilitating measures necessary for generic growth to be stimulated. An additional factor is that there are lingering concerns over the quality and reliability of supply.

The nature of generics companies

With the exception of Novartis, with its Sandoz generics subsidiary, no major pharmaceutical company is currently involved actively in the generics market. This subsidiary has been built up over the past decade so that in 2007 it accounted for about 20% of Novartis's total turnover.

However, in the past – most recently in the early 1990s – a number of major companies dabbled in generics. But most withdrew after only a few years, often making substantial losses in the process. The next largest pharmaceutical company to Novartis which persisted in generics, Merck KGaA, eventually sold off its generics division, to the leading US generics company Mylan, in 2007.

Generics companies are different in many ways to major pharmaceutical companies. The resources and time involved in what generics companies term 'R & D' is modest compared with those required to bring a NCE to the market; it typically takes about four years preparation for the US market. In contrast, pharmaceutical companies are geared to costly, long-term development of new products.

Generics companies tend to be intolerant of delays and setbacks. A move by several of the larger generics companies into NCE R & D around 2000 soon evaporated. Only a small minority proved capable of weathering the typical risks and setbacks of pharmaceutical R & D that they began to experience. The majority of leading Indian companies doing so had by 2008 found running an R & D operation and a generics operation within the same organisation incompatible. They have spun off their NCE R & D into separate companies or divisions.

Also, as far as the market is concerned, generics companies are of necessity much more short-termist in their ethos than pharmaceutical companies: the period of substantial profitability for a generic can be very limited – only a few months in some circumstances. The skills and experience required to be successful

in generics are, therefore, manifestly different from those needed to succeed in the conventional pharmaceutical industry.

Cost has to be foremost in the considerations of any generics company. This has traditionally been far from the case for pharmaceutical companies, where margins are far from modest. And even accounting for the increasing awareness of pharmaceutical companies of the need to be cost effective, they have still tended to concentrate much less than generics companies on cost issues.

Relative size of generics companies

To give an indication of the relative importance of generics companies, in 2006 several US companies deriving most of their business from generics were represented in the Top 100 global pharmaceutical companies. All appeared in the middle of the rankings. These were:

- Watson (No. 42)
- Mylan (No. 50)
- Barr (No. 58).

The biggest generics companies outside the US are:

- Stada (No. 47, Germany)
- Actavis (No. 51, Iceland)
- Gedeon Richter (No. 59, Hungary)
- Ranbaxy (No. 64, India).

All ranking data, Scrip 100 2007/08, pp 8 & 9, Informa Healthcare.

Biosimilar products

Introduction

We deal with this in some depth, as the future of biosimilars is currently a topical issue.

The term *biogeneric* has been used to define a generic form of a biological product that is patent expired. However, because exact copying of a biological is almost impossible, another term – *biosimilar* – is now being more frequently used to describe a product developed to compete with an original biological product after that product's patents have expired.

A key consideration for biosimilars is that, given the relatively complex nature of large-molecule generics compared with conventional small-molecule generics, substantially more data will be required in the USA and Europe to obtain regulatory approval. *Safety* and *interchangeability* are particular issues.

Manufacturing of biologicals reproducibly within specification is not easy – the composition can vary from batch to batch in a way that would not be acceptable with small-molecule generics. The only way to tell whether a biosimilar is acceptable in terms of efficacy as well as safety is to conduct clinical trials – which adds considerably to the time and expense of developing them compared with small-molecule generics. Hence, as some clinical evidence looks likely to be required in most parts of the developed world to obtain regulatory approval, the development time for biogenerics is at least twice as long as for small-molecule generics.