

Protecting patients not patents^{*}

The challenge

Groups working with the pharmaceutical industry to deliver cheaper drugs to the developing world have made significant progress over the past ten years, but cost constraints still limit access to drugs by the world's most disadvantaged populations. Development Chemicals Ltd is proposing a new approach to further reducing the price of life-saving drugs by establishing an efficient manufacturing unit for developing and producing APIs using low cost processes. Such a unit would be responsible for making APIs at the lowest possible cost for supply to those regions of the world where price continues to be a crucial factor in saving lives.

The Poor

“The poor are always with us” – a well-known biblical quote; but is this true today The “poor” are no longer with us here in the developed world but conveniently hidden, in the third world, mainly in Africa, out of sight and for most of us out of mind. Sure, we have poverty in all parts of the world, including the richest countries, but all is relative. But the really poor?

To illustrate this, take the richest man in the world; not today but back in 1836, when one Nathan Rothschild (of the banking dynasty) set out from London for a family wedding in Frankfurt.** His journey was made rather uncomfortable by the presence of a boil or abscess on his back, but he made the wedding nonetheless. The boil became inflamed and despite (or maybe because of), the finest medical care of the day within a month or so Nathan was dead. He died from an infection that today would not have been considered serious and would cost a few cents to cure. And he was the richest man in the world. That is a clear illustration of the truth of the opening quote in that 1836 at least, when the rich and poor did share the same world.

For the “western world” the industrial and scientific revolutions just starting to get up steam in 1836 have changed the picture completely. Nobody today from the very richest downwards, needs to die from a treatable disease costing but few a cents for the drugs.

But out of sight in the third world, for lack of (amongst other things) cheap drugs, people are dying at a rate of more than one a minute from malaria alone. This is true poverty.

Malaria

The final answer to malaria will not be from drugs alone. Better use of insecticides and public works, like the draining of swamps and constructing safe housing, will continue to be major ways to prevent disease. In the meantime, access to life-saving drugs for all is needed.

* With apologies to Dr. Yusuf Hamied of Cipla

** “The Wealth and Poverty of Nations” by David Landes. He makes the point that the growing disparity between rich and poor is by far the biggest threat to the future of mankind.

Volunteer doctors working in clinics in Africa are given expensive anti-malaria drugs themselves but they are not allowed to use these products for the treatment of the sick children in their care because of the cost. Of course many of these doctors end up handing out their own drugs but this of course is just a drop in the Ocean and ultimately counterproductive should the doctors get sick; better to have some care from a healthy doctor than none at all. This is the situation that we should try to address. Not to develop newer and more effective candidates (leave that to others) but to focus on what the pharma industry is particularly poor at: reducing the cost of existing products. And why is the pharma industry so poor at this, what in principle is a simple exercise? The industry used to be much better at this than it is today, so what is the problem? The reasons lie in the history and development of the pharmaceutical industry

The Pharma Industry

The history of some of the modern hi-tech “life science” leviathans, such as GSK and Merck, goes back to the old producers of patent quack remedies and food supplements (naturally they don’t want to talk about it too much!). However, the true origins of the research driven lifescience industries of today began with the early chemical industry, particularly dyestuffs (they don’t want to talk about this either – purveyors of quack medicines have a better image in today’s world than the chemical industry! – and this is part of the problem).

The first synthetic dyes were produced in the late 19th century. The modern industry grew up with a basic structure of today’s pharma and agchem industries – great numbers of research chemists producing vast numbers of compounds for testing, but at that time dyes were the target. When new compounds were discovered, scale up and manufacture on a chemical plant that has not really changed in design to this day. Virtually every piece of chemical equipment in a modern pharmaceutical factory can be traced back to equipment in the early dye plants. The connection with pharma is actually even closer, since one of the (tiny) uses for these new dyes was for staining microbe samples for the microscope. Erlich noticed that some dyes bound more strongly to the microbes than others and reasoned that, if the dye carried some sort of toxin specific to the microbe, it might be effective as an “antibiotic”. Since virtually all the health problems of the time were caused by these recently discovered microbes, this was an idea that led to some of the first synthetic drugs (Prontosil being the first). The trials in those days were not very sophisticated, often commencing with the discovery chemist eating some of the new product to make an initial toxicity check! Since that time, things have changed in detail, but the basic model has remained unchanged – make lots and compounds and test.

One of the basic problems of today is the very success of the early industry, which along with things like clean water supply and sewage disposal (probably more important than drugs), has virtually eliminated the big infectious killers of the Victorian age. The industry needed other targets in the Western world and they were not long in becoming apparent – the problems of affluence itself. The pharma industry soon realised that it was much better to treat the rich and much better not to actually cure anything (no point in destroying the market). This model has created a virtuous circle, in commercial terms, for the industry since the late 1970s. The main problems of the rich such as obesity, cardiovascular disease,

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depression (it helps to be rich to be depressed) lend themselves, not so much to an immediate cure, but to a lifelong regime of drug treatment to keep the condition at bay. Perfect.

So the pharma industry evolved to the model we have today. There is however only one problem in targeting the rich as your main market; if something goes wrong they have the resources to sue you. Hence the vast growth in regulatory bureaucracy, both within government agencies and within the industry itself, and the immense care and cost that precedes the launch of a new product. The price that we in the West are prepared to pay for this safety has led to the current structure of the industry today.

In rather simplistic terms the pharmaceutical industry can be split into three groups:

- Big pharma. The original giants much changed by constant takeovers, but these groups still offer the full package from discovering and developing novel drugs at great expense all the way to making and selling them. They are heavily dependent on “blockbuster” products for which they have the discovery patents and a period of monopoly.
- Research-based companies. These relatively new companies (usually founded by ex big pharma people) are just doing the discovery and early development in the hope that they will find a promising product and that big pharma will come along (with big cheque book) and make them rich in a license deal. Since these organisations do not manufacture drugs they do not really feature in this narrative. The problem is the next group.
- The generics. Generic companies do little or no discovery work but wait for big pharma blockbuster patents to expire, when they jump in with the same product and cut the price. In order to do this the most vital requirement is to ensure that your product will meet the regulatory requirements as already established

When a new blockbuster from big pharma is launched there will probably be less than half of the patent (monopoly) period left, and so during this time the company will set up a price structure that is remarkable by the standards of any other manufacturing sector. Manufacturing costs will typically be around 10% or less of the selling price – or a 90% gross margin. The justification for this fantastic margin, according to industry propaganda, is the huge cost of research and development. This is part of the reason, but the other costs are the enormous regulatory burdens, the huge legal costs to defend and hopefully extend patent lifetimes and the enormous sales budgets (to persuade people that they need treatment and this is the drug for you!) in the market that all pharma companies must succeed in, the US. The net result of this situation is that many major pharmaceutical products are made using sub-optimal technology since there is no real incentive (at least for the originator) to have a very efficient process.

Long before the patent runs out the generic companies are gathering; to be ready to get into the market as soon as the day arrives when they have the patent all clear. It is the established belief in the industry that it is vital to be the first or second generic copy on the market since they are the ones that will capture the biggest slice from the big pharma brand. The generic companies do need to be more efficient than big pharma, since they are certainly going to see the price come down, but they have no

interest in seeing really low prices – in fact quite the contrary, they would like to keep the price as high as possible, particularly with a view to capturing a slice of the all-important US market where prices are kept extremely high by world standards. In order to get a slice of this market the generic companies will spend sometimes even more than big pharma on legal battles (to prevent patent extensions this time) and they have the same vested interest in maintaining the regulatory barriers since that is the best way to keep out the other competitors. Whilst manufacturing efficiency may be better than big pharma it is still the poor relation compared to regulatory, legal and marketing operations. In many ways the generic companies have even less excuse for their (still) big margins. Big pharma, despite all the faults, do provide virtually all the innovation and discovery of new products, whereas the generic industry makes a zero contribution in this area.

So the basic problem is that the industry has grown up focusing on diseases of the rich world, and with no real interest in producing low cost products, since regulatory barriers effectively stifle real competition.

There is of course no overriding imperative for the pharma industry to operate on a higher moral plane than any other sector. They are in business solely to make money for their shareholders and that should not in itself attract any criticism. The problem is the structure of the industry that this situation has created, particularly at the manufacturing level. Big pharma is in business principally for the period of monopoly sales for their blockbuster products and the generics are looking to carve up the market when the patent expires in such a way as to minimize the price reductions. Both are highly focused on markets in the developed world.

Recent developments have not improved the situation. Big pharma companies have become fixated almost solely on their stock price and for whatever reasons seem to have lost the ability to discover enough new blockbusters. One result of this is that they have now entered the generic markets themselves (unheard of not so long ago). This is hardly likely to improve overall manufacturing efficiency of the sector.

Process development

So, this is the problem; Improve manufacturing efficiencies so that certain drugs can be made much more cheaply.

The first stage of manufacturing in any chemical operation is process development. When a new molecule is selected for scale up and production in pharma, the cost of manufacture is just one factor to be looked at in development. In big pharma the greatest priority is to make sure material is ready for the next pre-clinical or clinical trial, and since the product will probably never make it to the market anyway why waste time and money on exploring a much more efficient manufacturing route? Most new pharmaceutical candidates are already very challenging from a process development perspective, with multiple chiral centres and so forth and just to establish a practical route to produce gram and kilogram quantities for development is not a trivial task by any means. As the compound moves forward in development regulatory issues make radical modifications to the process more and more difficult and the net result is inevitably a compromise. In the case of a generic product, the process development

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situation is clearer since there is now no doubt about the product reaching the market and that the cost of production will be more important. More important still however will be the need to “not rock the boat” with any regulatory issues which might delay the launch.

In principle what DCL is proposing to do is to bring the process development philosophy from other chemistry based sectors where cost of production is paramount, to bear on the problems of pharma. When a new product is proposed in say the agrochemical sector, cost is almost always the key factor. What will this molecule cost to make on a full scale? If these costs are met will the market buy it? In fact a major reason for the failure of many agchem products in development is failure to meet cost targets – a quite rare situation in pharma. And cost is the only real yardstick for process development, not scientific excellence/ interest, not environmental “greenness” – just cost. The cost of making the product to the right quality and within the boundaries of legal (and safe) operation.

Once you have a cost effective process then you are nearly there, and the rest is a matter of good chemical engineering design. You then need a suitable plant to implement the process with clear sales value targets whilst maintaining correct quality standards. Then, and this is a key point in this concept, generate the selling price by adding a margin to the cost, which is of course the basic model for most of manufacturing industry.

Proposed facility

Development Chemicals Ltd is a process R&D operation based in the UK. The company has been active in carrying out process development for anti-malarial products and other API's for neglected disease areas with the support of agencies such as MMV (Geneva). We are now proposing to establish a facility to manufacture a small range of key API's for malaria and other serious tropical diseases for which low cost drugs would be of major benefit and in which a combination of state of the art process development and a different approach to costing would be used. This plant would only carry out the final cGMP stages, with regulatory starting materials produced by DCL's existing network of suppliers in India, China and elsewhere. The current situation in the pharma industry in North America and Western Europe is very favourable to such a concept at the present time given that there is both a large inventory of high quality used manufacturing plant available and more importantly a large group of motivated and talented people who have up to recently been employed in major pharma groups but have fallen victim to the current fashion for “re-organisation.” DCL is now exploring support for this venture which will most likely be a combination of grants and commercial finance. A number of sites are under consideration for such a facility which would not only form a centre of excellence for process development but represent an attempt to make a practical contribution to one of the major problems facing all of us.

We firmly believe that such a venture is worthy of financial support. This initiative will be, in effect, an attempt to use enlightened market forces using a standard chemical manufacturing model of sales price equals manufacturing cost plus margin. As discussed above, this is not the model for the current pharma sector, which starts from the premise “what price will the market stand?” This “traditional” approach

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has worked well for the western world's pharmaceutical industry, but is a disaster for poor individuals and countries where the market will stand, to put it bluntly, one child dying of malaria every 45 seconds.

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