DISRUPTING PHARMA—ONLY POLITICIANS CAN DO IT, HERE'S WHY AND HOW

THINGS ARE OUT OF CONTROL IN PHARMA

"Obama blames high drug prices on companies too worried about profits"
"Hillary Clinton Unveils Plan to Address 'Excessive' Increases in Drug Prices"
"Trump Calls Drug Pricing 'Astronomical' and Promises Changes" (subsequently watered down)

Politicians have been bearing down hard on Pharma pricing for some years now. Sadly however, sky-rocketing drug prices are just the tip of a massive iceberg. We see $bns spent pushing brands on health-care professionals, the many clinical trial failures, $bn litigation over damaging side-effects, me-too drugs, shortages, counterfeiting, price gouging—a seemingly endless list of debilitating issues (References: [1] [2] [3] [4] [5] [6] [7] [8] [9] [10] [11]).

Surely, if any industry needs disrupting, it's Pharma?

Yes, and pundits are touting Amazon, Google, Apple, IBM, Microsoft and others as the possible source of disruption. This paper brands that rubbish, and explains why **ONLY** politicians can make it happen.

Return to the battle of the anti-ulcer drugs

In November 1976, Smith Kline & French (SK&F) launched Tagamet, a drug to combat stomach ulcers. It quickly took off and was dubbed the world's first 'blockbuster' drug (≥ $1 Bn annual sales).

Glaxo launched a competitor product, Zantac, in 1981 and immediately targeted reportedly minor side-effects of Tagamet to pitch their case to doctors. By 1987, Zantac had become the world's biggest-selling prescription drug, outselling Tagamet 3:1 at one point[12].

This was the first example of clever targeting capturing competitor markets, and it stimulated phenomenal growth in the therapeutic area; the profits were immense for both companies, on sales of tens of billions of dollars. The beginning of a lucrative strategy for the industry was cast.

Glaxo's formula gets the thumbs up

Large, profitable pharmaceutical companies (Big Pharma) and their Investors were mightily impressed by what Glaxo had achieved. Even the CEO of SK&F congratulated them on their win.

Armed with this apparently powerful strategic model, Big Pharma resolved to beef up sales & marketing, awaiting molecules (also known as compounds) coming down the pipe. Discovery research grew like topsy, as great libraries of patented molecules were required to feed the hungry marketing machine.

Expert statisticians and medics were hired to help the marketers frame the messages to doctors. Regulatory affairs departments were expanded to be sure of keeping on the right side of the regulators, just.

So the scene was set. Sales & marketing, with their supporting cast, were poised ready for the next blockbuster molecule to come down the pipe. Discovery research was out there, plotting theories on why a molecule would work, modelling and patenting them in great quantities and stuffing prime suspects into the upstream end of the pipe.

In the investor community, however, there was emerging realisation that not much was actually making its way out of the pipe. The prospect of being lumbered with huge fixed costs if a drug failed was a serious concern.

Coincidentally, during the '80s, other sectors were outsourcing 'non-core activities', claiming significant benefits in risk reduction, plus lower costs to boot. That seemed like the perfect solution.

Discovery research and marketing were considered core activities. Running clinical trials, manufacturing and testing materials, movement and storage, making active ingredients and patient dosages were all classed as non-core…

…and so the cull began.

Outsourcing begins in earnest

The exact sequence of events isn't easy to pin down, but the results were unmistakable—masses of workers were shown the door and thousands of facilities went up for sale.

Ousted senior execs looking for pastures new put the dumped assets to good use. They set up small companies (dubbed biotech at the time, we will call them SDDs, small drug developers) developing drugs to either sell to Big Pharma or try to get to market themselves.

The CEOs in SDDs were making a persuasive case to be the engine house of drug discovery, citing less bureaucracy and shorter chains of command. Investors liked the sound of it and started pumping money in.

Meanwhile, other exiting senior execs joined together and bought up the facilities, funded by a different cadre of investors. These companies provided SDDs with services in exchange for a fee, under contract. These became known as contract development and manufacturing organisations (CDMOs) and contract research organisations (CROs).

Many of the rest of the redundant staff became consultants. Not the McKinsey kind, more former employees selling their skills back into the industry under contracts of varying length. I became one of them.

Also on the agenda was the tricky business of supplying hospitals and pharmacies. Handling customer complaints and dealing with ever more frequent deliveries were not deemed core and Big Pharma handed over all of its warehousing and distribution assets to gratefully receiving wholesalers.

Similarly, specialist third party logistics providers (3PLs) grew their businesses helping with the burgeoning volumes of materials and products that needed to be stored, and transported around the globe.

The final arm of the strategy was out-throwing; the practice of dropping existing products once the patent expired, as they didn't meet the sumptuous ROI targets the branded versions had enjoyed.

Up sprung companies with more modest profit aspirations working to much tighter margins, copying the originals. This gave rise to the generics industry, where, at last, competition was going to save the day, or was it?

How did the dynamic pan out?

The number of SDDs began to accelerate as the potential rewards in doing a licensing deal with Big Pharma were immense. These new boys on the block were developing drugs themselves, hoping to eventually hand the baton on to Big Pharma.

There was similar growth in numbers for the CDMO/CROs, since business was brisk, as both the SDDs and Big Pharma increasingly needed their services.

The Drug Price Competition and Patent Term Restoration Act of 1984 ("the Hatch-Waxman Act") gave a welcome boost to the use of generics and this, in turn, was more business for the CDMO/CRO's.

With the growth of biologics, more companies entered the fray. Biosimilars, the generic equivalent in biologics, were attempting to capture innovator markets as patent expiry loomed. Biobetters were aiming to improve on what had gone before. Again, they needed the services of CDMO/CROs.

The ever increasing availability of services to cover almost every aspect of drug development encouraged universities to 'spin out' their research ideas into SDDs on the trail of Big Pharma attention and licensing deals. Government grants and funded bodies were set-up to support progress.

All this time, the contractors had began consolidating, egged on by private equity regarding service providers as high potential, less risky investments; and all was not rosy in the Big Pharma garden.

When was there a whiff of things going awry?

The first piece of definitive evidence of problems emerged in 2006. The United States Government Accountability Office (US GAO) issued a report, which amongst other things, showed a chart of the failure rates in the life of a prescription drug[13]. 4 out of every 5 drugs entering clinical trials failed. Of the 5 that entered clinical trials, 250 had to go through extensive (and expensive) testing pre-clinic to find suitable candidates. The one drug that made it to market consumed 10,000 molecules in its making.

In 2012, Joseph A. DiMasi, PhD, of Tuft's University, presented at Pharma Integrates 2012, confirming the US GAO figures above, suggesting things had gotten worse since then.

So the valley of death, as it became known, was swallowing up most of the molecules entering development. It was common place to read of drugs failing in phase III trials, where the hopes and dreams of patients were dashed. Hundreds of thousands of animals tortured and slaughtered, with no contribution to medical science. Billions of dollars poured down the drain. The sickening cost of failure.

Where are we today?

Big Pharma is a dried up prune compared to the fulsome plum it used to be. It has retrenched into opposite ends of the prescription drug lifecycle, leaving most of the work of testing, developing, making, storing, moving and distributing drugs to third parties.

On the other side of the fence, the fledgling service providers that were, flew the nest years ago and grew into fully formed adults, some soaring like eagles.

CROs have been and still are consolidating, becoming big, powerful providers of clinical and non-clinical services. [14]

Massive consolidation has also taken place in the CDMO world, and media evidence suggests they are moving into additional areas of the value chain.[15] [16]

The specialist 3PL's have also been part of the consolidation, as the two main players have been acquired by giant corporations, one from inside Pharma and one from outside. [17] [18]

The finished product distributors of Pharma products are now mega corporations, on the back of, yes, you guessed it, consolidation. Just three share over 80% of the market on each side of the pond. There has been forward integration (pharmacies) and reverse integration (logistics specialists) going on for some time and also moves into broader service offerings to the industry.

The generics industry has grown enormously on the back of payer demands for cheaper drugs. Up to 90% of drugs now sold in the US and UK are generic. Ironically, in later times, the intense competition for out-of-patent drugs has subsided, which has led to spiralling rises in generic drug prices. This again has been attributed to M&A activity leading to far less, bigger players on the field being able to pick and chose what they supply; with the ever present shortages adding to the hikes.

This is a very different Big Pharma from the days of Tagamet and Zantac.

The painful analysis

It all started with Glaxo's success inadvertently creating an illusion that fooled an entire industry, including itself.

As accidental illusionist, Glaxo did what magicians do. It deflected audience eyes away from the hand enabling the magic, onto the hand performing the show. The illusion was met with thunderous applause, as it unfolded before Big Pharma's very eyes. The audience left, filled with the potential of repeating the magic for themselves.

Returning to the real world, the illusion can be explained using the lifecycle of a prescription medicine shown in Figure 1 below:

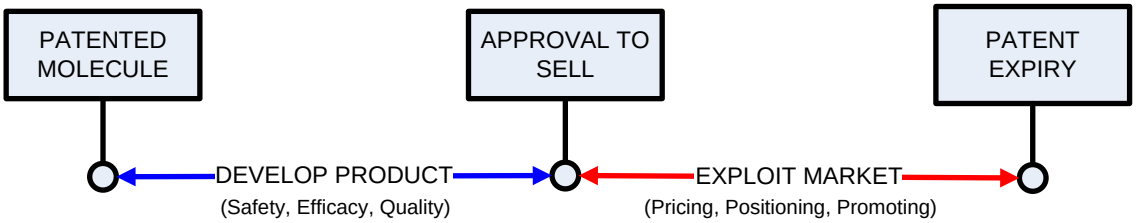

FIGURE 1 LIFECYCLE OF A PRESCRIPTION MEDICINE
(NB: Patent life is approximately 20 years from date granted)

There were, and still are, three key milestone dates—patent award, regulatory approval and expiration of the patent; and two broad phases—product development and market exploitation. Glaxo's success turned eyes towards the period between approval and expiry, the market exploitation phase (red line), and then leftwards to the all important patent award.

The industry looked toward the blue line of product development and could only see routine drudge, cost drain and risk exposure. It apparently seemed reasonable to toss much of product development out the boat and leave it to others. The real 'science' was perceived to be a numbers game in discovery, where serendipity (remember penicillin?) played a leading role.

Zantac had taken just five years to get to market and with the technology breakthroughs in molecular modelling and other computational techniques, finding promising molecules could only become easier over time (really?).

This shone a spotlight onto remaining patent life, the time available to wring the market. Consciously or unconsciously, Big Pharma heads turned towards the thing that was eating up the remaining life—product development.

Developers' behaviour reflected the heat heading their way. No-one wanted to be caught mouthing "wait a minute; I'm not ready to move on". The mantra handed down was "every day's delay is $2M in lost sales". This became a useful stick to beat people with, metaphorically, of course.

Any developer raising a red flag on the suitability of a molecule for the clinic and market risked a slapped wrist, so they didn't say anything and got on with their jobs.

Once a molecule entered the pipe, there was no way back. No time for any iterative dialogue between discoverers and developers, looking at alternatives if issues were found. The discoverers were off to other searches for compounds with blockbuster potential, sorry; I mean drugs to treat patients with unmet medical needs.

This was the first dagger into Pharma's heart—playing the numbers game, hoping for the best (by the way, Alexander Fleming discovered a mould that fought bacteria; he didn't isolate the active ingredient or patent the process to make it at commercial scale, that was an ex-government employee).

The second was outsourcing people and facilities, and the third was in-sourcing molecules.

On outsourcing, Big Pharma had not heard about the pitfalls of inappropriate outsourcing of core competencies (see Andrew Cox) demonstrated by Boeing's excursion into outsourcing of product development for the Dreamliner[19].

Boeing was attempting to do the same as Pharma, which was to "shift the economic risk onto those [their] suppliers."

Previously, Boeing had "maintained tight control over the design" and provided detailed specifications to suppliers. The telling comment is "by outsourcing the design and the manufacturing, Boeing lost control of the development process." Boeing eventually recovered by choking back their outsourced model, but nor without major issues of delays and overspend[20].

Big Pharma was not so lucky. It has fallen into all of the pits and discovered a few more besides!

Then there were the foreign molecules arriving at Big Pharma's door. The ones licensed-in went into the pipe, and no amount of due diligence could have identified all the various nuances of the molecule's treatment whilst with its birthing parents. Sometimes, remedial work was required and often there was no time for that, the show had to go on and molecules moved on to become one of the many deals that went awry.

It was these three factors that did the damage:

1. Basket cases launched into development.
2. Handing over critical assets to third parties.
3. Outsourcing drug development to SDDs.

These combined created the valley of death we see today, which over time became the patent cliff.

What is Pharma doing about it?

In response, Big Pharma is employing a number of tactics to maintain revenues from the declining pipeline of blockbusters. Health Economics and Outcomes Research (HEOR) has become a new tool in the box. The reluctance of payers to stump up for the eye watering price proposals has given rise to market access groups, tasked with justifying why prices are so high, based on HEOR arguments.

Also in favour is targeting perceived less challenging regulatory environments and patient populations—rare diseases, orphan indications and all things cancer. The unfortunate side-effect of this is that prices have to be astronomic because of the very small volumes.

Pharma, it seems, is playing the same tune on a different instrument. No sign of recognition that all is not well in the rose garden. So how do we get to the bottom of this, then?

What was at the bottom of all this?

The discipline of Systems Thinking was developed to get to the bottom of issues emerging in complex, interconnected systems of people and resources, working to a defined purpose. We can borrow a few of the principles here to help get our arms around this problem, namely:

1. Rarely do individuals set out to bring companies and industries down.
2. Rewards drive behaviours, good and bad.
3. Cause and effect are almost never in the same place.

Point 1 tells us it has been the system that has done the damage, fuelled by blockbuster returns for all, as per Point 2. Point 3 teaches us to look beyond the symptoms being exhibited in the field of play, towards the source of the evil.

Rather than bang on with theory, let's take a practical example by taking the same journey back in time, to the days of Tagamet and Zantac.

The truth behind the illusion

The invisible hand performing the illusion was SK&F's development effort in bringing Tagamet to market.

In 1964, SK&F set up an acid secretion programme in its UK arm, with a vastly experienced team from across the drug development disciplines. They were pioneers of rational drug design, whereby a drug was designed based on knowledge of a biological target known as a receptor. This was in contrast to the industry tradition of trial-and-error testing according to the serendipity principle.

Over the pond at SK&F was another set of gifted individuals developing the PROCESS to make the drug as a commercial proposition. This in-company collaboration was reported to have worked incredibly well.

One account, by the American Chemistry Society (ACS) commented on the development effort "[this] is a story of single-minded commitment by a group of creative scientists working in close collaboration in the United Kingdom. The process of research and development for economical production of the resulting drug, cimetidine [Tagamet], was the work of equally creative scientists working in the United States." [21]

The head of the cimetidine programme, Sir James Black, later received the Nobel Prize for his drug research. Sir David Jack, who was responsible for Glaxo's development effort in bringing Zantac to market in only 5 years, was quoted as saying:

"the development of Zantac had not been in the same order of inspired breakthrough as the research which produced Tagamet… It's not necessary to shake the earth on its axis to make money in this industry. We simply improved on James Black's product by choosing a substance with a cleaner reaction." [22]

So here is the illusion laid bare. The real success in the case study was the fully integrated drug development effort WITHIN THE SAME COMPANY. A patent was awarded for the PROCESS at commercial scale, not a few grams of compound in a test tube.

This is not the end of it. Glaxo may arguably have achieved something of comparable importance. The comment above from Sir David Jack suggests they were able to improve the side effect profile of an existing drug, by altering the production process. No deep science, or complex molecular modelling, nor artificial intelligence or digital gizmos, just good old fashioned common sense.

To lean on one last ST principle to wrap up, we come to the principle behind the proposed solution:

"Don't fight the system, change the rules and the system will change itself"

This is where politicians come in

The conclusion is that in the quest to exploit remaining patent life, Big Pharma has paid scant attention to the fundamentals of every single industry known to man. Developing products is for grown ups. A medicine is no less a development challenge that an aircraft, automobile, submarine or anything else.

The award of a patent for a few grams of compound, a theory and a chemical structure, blinds the industry to the enormity of the task ahead. This has resulted in the issues we face today; and the future?

The emerging fields of cell therapy, gene therapy, tissue engineering, precision medicine, stratified medicine, patient-centred therapies, call them what you will, are an order of magnitude more challenging. Their progress will be critically compromised unless the rules are changed…

…and the change required is very simple. Patents should require more evidence that a molecule can be converted into a product on the market AT THE TIME OF PATENT APPLICATION. Dare I say we call it a prototype?

Next time we will explore the way to do it.

H.G Rees 15/08/17

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