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What next for pharma?

Future themes in research, regulatory, competition and mergers and acquisitions

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1 Introduction

According to a recent study, pharmaceuticals is among the world's three most 'uncertain' industries[1]. To discuss how the sector can address such volatility, KPMG gathered a number of pharmaceutical industry leaders at a workshop in Frankfurt in late 2014.

Chris Stirling

Chair of Global Life Sciences, KPMG in the UK

Vir Lakshman

Head of Chemicals & Pharmaceuticals, KPMG in Germany

Innovation is the lifeblood of life sciences companies, and Professor Sir Stephen Bloom of Imperial College London, looked at what lies ahead for research, arguing for a new, 'collaborative contract' between academia and industry.

Regulations are an intrinsic part of the drug development process, but can they be better harnessed to enable vital therapies to come to market earlier? This was the question posed by Professor Vincent Lawton, CBE, who is a Non-Executive Director of the Medicines and Healthcare Products Regulatory Agency (MHRA).

Next up was KPMG in the UK's Head of Creative Thinking, Adam Bates, who painted a vivid picture of the disruption that is intensifying competition in the sector, with new entrants from a number of converging industries.

In the final presentation, Rupert Hill, Managing Director of Greenhill & Co. International, assessed the current deal environment, concluding that appetite for larger cross-border transactions and asset swaps remains strong, but that tax inversions may have peaked.

The workshop stimulated vigorous debate on issues that are critical to the future health of the life sciences sector, and we would like to thank all those that attended.

1 *The Industries Plagued by the Most Uncertainty,* Harvard Business Review, 11 September 2014.

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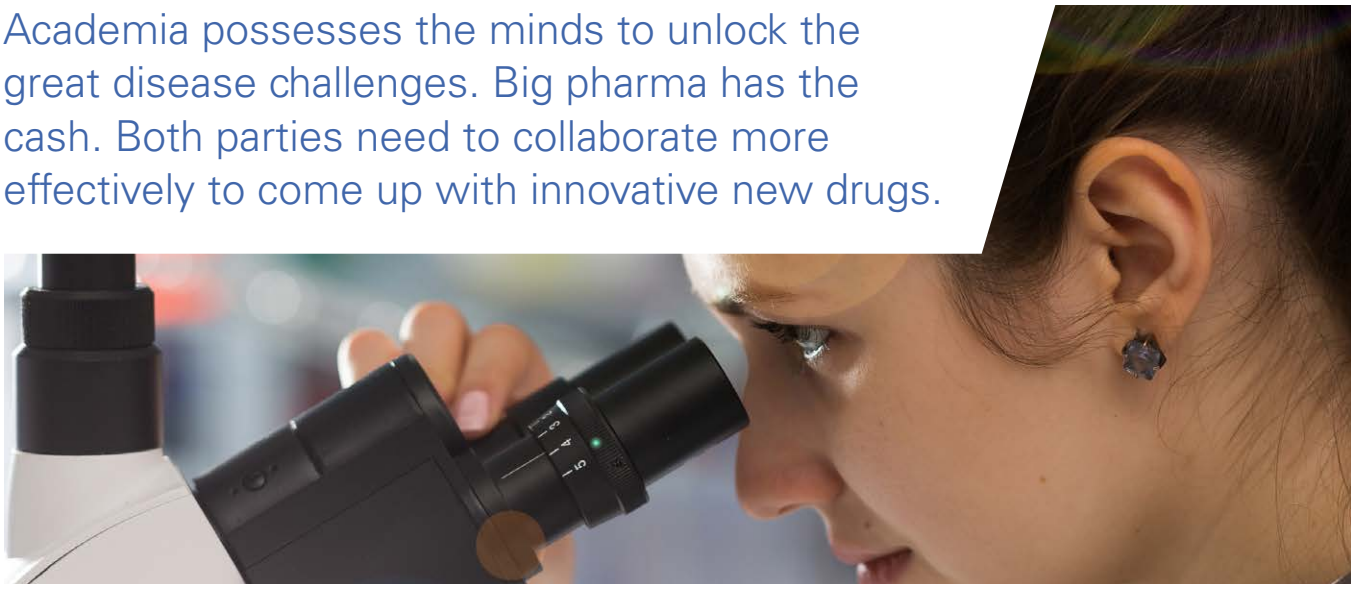
The future shape of research

Academia possesses the minds to unlock the great disease challenges. Big pharma has the cash. Both parties need to collaborate more effectively to come up with innovative new drugs.



Professor Sir Stephen Bloom

Imperial College London

Three forces are coming together to create a perfect storm in the ocean of life sciences. Firstly, the epidemic of chronic disease is overwhelming health services and putting intense pressure on budgets, with the obesity pandemic threatening to reduce life expectancy in developed countries. Obesity is a huge, indirect killer, with sufferers more likely to get diabetes, strokes, heart attacks, cancer and Alzheimer's disease.

At the same time a host of exciting new areas of science are opening up possibilities for discovery, such as genomics, genetics/epigenetics, metabolome, enzyme inhibition/activation, nanomedicine, stem cells and cellular transplants. Many scientists are exploring these routes to try to come up with more personalised treatments.

Yet, thirdly, and worryingly, the effectiveness of traditional life sciences research is under question, with a limited number of new drugs emerging, and a patchy record of collaboration between big pharma, universities and start-ups.

Given that academia is likely to be the prime source of future breakthroughs, how can the pharmaceutical industry better harness these discoveries to address chronic diseases and turn a healthy profit?

Large, corporate, top-down research structures tend to lack the passion to see ideas through, while unsupervised work in academia is often short on commercial discipline.

A questionable track record

No one is pretending that there is an easy answer to the research conundrum. Success is dependent on deep pockets, tenacity and resilience, and, in some cases, a hefty dose of luck. It sometimes seems as if research directors' positions are about as stable as the average Premier League football manager!

From an institutional perspective, top-down structures dominated by a few science administrators tend to lack the passion necessary to see an idea through to the end. And, although industry is not coming up with sufficient new discoveries, unsupervised work in academia often lacks the discipline to push through to a commercially viable outcome, with a high level of wastage.

Research fails for many reasons, including insufficient demand for the compound, lack of novelty, excess competition in the field, limited potency of the drug, poor absorption, toxicity, side effects and poor storage stability.

Relationships between life sciences companies and universities have a chequered history, with the former concerned over lack of focus and business nous among academics, and the latter suspicious that the firm is simply trying to steal their intellectual property. Venture capitalists have also been frustrated by the long waits and uncertain returns from their investments in biotech.

Pharma companies and other public and private financing bodies recognise the inherent potential within universities, where many of today's drugs were initially conceived.

Towards new models of collaboration

Despite concerns over clashing cultures, pharma companies and other public and private financing bodies recognise the inherent potential within universities, where many of today's drugs were initially conceived.

The UK's government-funded Medical Research Council (MRC) exists to further innovation, and continues to recognise the undisputed potential within academia, including a £3.7 million venture with the Universities of Liverpool and Manchester, to tackle dementia. The MRC is also collaborating with Novartis, Pfizer, Merck and the association of the British Pharmaceutical Industry, as well with AstraZeneca's Centre for Lead Discovery, which gives access to the pharma giant's 1.9 million screening collection and technology platforms, with MRC-funded scientists working alongside AstraZeneca researchers on selected projects.

A team from Imperial College, London is studying how appetite control can combat obesity. The potential solutions include a microchip that send signals to the brain to halt the urge to eat, and a treatment that combines two hormones to reduce appetite.

A company called Zihipp, half owned by the university, has been formed to manage the new treatment, with MRC funding.

Among other initiatives is a £29 million, 5-year research programme into drug-induced liver damage, funded via a public/private partnership by the European Innovative Medicines Initiative (IMI) and the European Federation of Pharmaceutical Industries and Associations (EFPIA).

There is also an encouraging change in the way that academic research is evaluated, with a shift away from pure scientific papers towards activities that could attract funding and, ultimately, a commercial return.

Governments everywhere recognise that a healthier population consumes less healthcare budget, and are keen to promote – and to some extent invest in – promising research. Scientists in universities have a burning desire to solve today's pressing health challenges, but need to acknowledge the difference between a brilliant idea and a sound, marketable business proposition. Successful institutions such as Stanford have proved that money follows true innovations, and the life sciences sector needs to find ways to make collaboration work more effectively, by creating effective joint teams with common cultures and mutual goals.

Professor Stephen Bloom is the Head of Division for Diabetes, Endocrinology and Metabolism, Chair of the academic Section of Endocrinology and Investigative Medicine at Imperial College London and Lead Clinician for Clinical Chemistry at Imperial College Healthcare NHS Trust.

Regulation as a driver of innovation – not a barrier

A more collaborative approach to the approval process can help speed up the development of new drugs and give patients urgently needed therapies sooner.

Professor Vincent Lawton, CBE

Non-Executive Director, Medicines and Healthcare Products Regulatory Agency (MHRA), Chairman, Addex Pharmaceuticals S.A.

The announcement in September 2014 that an innovative cell therapy for cancer had become the first designated as 'promising' is a welcome step towards getting medicines to patients quicker. DCVax-L, developed by US-based pharmaceutical company Northwest Biotherapeutics Inc was awarded the UK's new 'Promising Innovative Medicine' (PIM) designation – the initial step in the Early Access to Medicines Scheme (EAMS), which aims to increase patient access to medicines where there is an unmet medical need.

Such initiatives provide a boost to companies striving to attract capital during drug development, and demonstrate regulators' desire to be a central and positive part of the innovation cycle.

Pharma companies and regulators share remarkably similar missions: to contribute to improved public health by providing safe, new, high quality, efficacious and affordable drugs. Regulators are increasingly focusing on accelerating the speed of approval without compromising any of these principles. This means applying a 'light touch' approach for urgently needed therapies, and encouraging more communication with the researchers, to identify suspect compounds early, and offer advice on optimising the prospects of winning approval and setting appropriate prices.

Dialogue is all-important, to overcome any mutual negative perceptions, with life sciences players sometimes critical of excessive regulatory red tape, and regulators concerned over incomplete or unclear approval submissions.

Initiatives such as the UK's Early Access to Medicines Scheme demonstrate regulators' desire to be a central and positive part of the innovation cycle.

Facilitating progress

With growing pressure on research budgets, the UK's Medicines and Healthcare Products Regulatory Agency (MHRA) has acknowledged the need to sustain a healthy pipeline of new products. The rise in approved new molecules in 2013 appears to be a blip in an otherwise downward trend that has lasted well over a decade.

Approval times differ by region, with Europe (median of 489 days) considerably slower than Japan or the US, with a median of 306 and 304 days respectively.

The MHRA's main tools to facilitate licensing include conditional licensing, licensing under exceptional circumstances, advance therapies regulation, accelerated assessment, adaptive licensing and the aforementioned Early Access to Medicines Scheme (EAMS).

Adaptive licensing – sometimes called staggered approval or progressive licensing – offers the chance for early authorisation, where the need is particularly urgent, for example, for life threatening or debilitating conditions. At the same time, evidence can be gathered to enable access to a broader population.

By encouraging collaboration, the MHRA aims to ease the approval process, offering pharma companies a number of routes to consultation and discussion, including its Innovation Office and scientific advice service. At the same time, it also seeks to be more proactive and responsive, by anticipating problems and acting and communicating rapidly and effectively.

The MHRA also works with the European Medicines Agency, to coordinate regulatory approvals and ensure that the UK maintains an approach that meets all stakeholder goals.

The US Food And Drug Administration (FDA) appears to be making positive progress. Of the 27 new compounds approved in 2013, 37 percent were in the 'fast track' category (average time less than 190 days), a similar proportion were given 'priority review,' (where the review aims to takes 6 months against a standard of 10 months), and seven percent of drugs for serious or life threatening illnesses were granted 'accelerated' approval (which could be as quick as 150-days).

Of the 27 new compounds approved by the FDA in 2013, 37 percent were in the 'fast track' category.

Notably, in 2013, 33 percent of FDA approvals were 'first in class' or 'orphan' drugs not used before.

FDA Commissioner, Margaret 'Peggy' Hamburg is not resting on her laurels, and in October 2014 stated that the organization was to undergo significant changes, with a more coherent policy and simpler management structure, and greater focus on prevention. There is to be greater specialisation across inspection and compliance functions, better training for FDA employees, and improved use of laboratories.

Such moves are a sign that regulators are adapting to a new healthcare landscape, where personalised, targeted medicines are aimed at smaller populations, calling for more specialised skills among regulatory staff. Pharmaceutical companies whose products are approved for sale in the European Union will soon have to make all clinical data supporting the approval of their medicines freely available to the public. Such transparency should raise the standards of approval submissions, which in turn should speed up the overall process. And, with expanding and accessible banks of historic clinical trial data, it should be possible to test and assess the performance and safety of drugs faster and more accurately.

An innovation-friendly environment is good for the patient, good for the life sciences industry and good for the nation, which benefits from a healthier workforce, attracts inward investment and builds stronger domestic businesses. By easing the path to approval, while maintaining safety and quality, regulators everywhere can contribute to a thriving healthcare sector.

Professor Vincent Lawton CBE was previously Managing Director of MSD UK Ltd & Sr. VP MSD Europe Inc. with whom he worked for 26 years in senior positions across Europe the US & Canada. He was subsequently Sr. StrategyAdvisor, Faculty of Medicine, Imperial College London.

Adapting to a disruptive environment

With the life sciences sector highly attractive to new entrants from converging industries, established players require agility to form new business models that deliver more innovation, faster.

Adam Bates

Head of Creative Thinking,
KPMG in the UK

The pharmaceutical, and indeed the wider business environment, is changing at an accelerating rate. Rapid homogenisation of markets and expansion of emerging nations is opening up huge new opportunities, particularly among the fast-growing, aspirational middle classes.

At the same time, technological advances are dramatically cutting the cost of processing and storing data. In 1981 a 10 megabyte hard-drive cost 2350 pounds (£); the equivalent of £250 million per terabyte. Today you can pick up a terabyte hard-drive for under £40 – six million times cheaper.

Fast, ubiquitous connectivity is changing the way people and organisations interact, and opening doors for entrepreneurs to create new markets and/or enter new ones, to quickly grab significant shares.

Such heightened competition is sweeping out the old guard of established companies, and ushering in new kids on the block, who in turn soon become vulnerable. Between 1958 and 2012, the average age of a company on the Standard & Poors (S&P) 500 index plummeted from 61 years to just 18 years. At this rate, three-quarters of the current index will be displaced by 2027[2].

As instability becomes the norm, large companies' customers and suppliers will change continually, leading to increased uncertainty.

At the current rate of change, three-quarters of the current S&P 500 index will be replaced by 2027.

2 *Creative Destruction Whips through Corporate America*, INNOSIGHT Executive Briefing, Winter 2012.

The past is no longer a reliable guide to the future

It is not just big business that is under threat. Research by the Oxford Martin School suggests that almost half of all jobs in the US are considered to be in a 'high risk' category, and could be automated within the next couple of decades[3]. As people get replaced by robots and computers, new occupations such as drone pilots, urban farmers and robot counsellors will emerge. In our lifetimes, bus conductors, meter readers, petrol station attendants, telephone operators, milkmen and chimney sweeps have all become redundant – a trend that is set to continue at a much faster pace.

All perceived wisdom is under question. At the tail end of the last century it was widely accepted that 'peak oil' – the maximum rate of extraction – was imminent, heralding a terminal decline. However, 'fracking' and other new methods have enabled oil production to continue to climb, with 2013 output 20 percent above 1999 levels[4], and a damaging plunge in the price of oil to over-production.

A recent Harvard Business Review study into technological and demand uncertainty revealed that, between 2002 and 2011, two of the top three most 'uncertain' sectors were pharmaceuticals and medical equipment; the other being software[5]. (Technological uncertainty was measured in average R&D expenditures as a percentage of sales, while demand uncertainty was measured by industry revenue volatility/change, as well as the percentage of firms entering or exiting the sector).

These changes are laying the ground for new and diverse competitors to enter the healthcare sector. Telecommunications companies like Australia's Telstra are investing in e-health, to connect patients and providers and enable more care in the home and community[6]. Danone has a significant medical nutrition division, and Fitbit offers a range of wearable devices that help people track their fitness and wellness levels. New start-ups are making rapid inroads, as evidenced by AliveCor's mobile electrocardiogram, which can be bought for around £125[7].

If existing life sciences players fail to adapt to uncertainty, they may quickly be left behind. As well as keeping a close watch on key trends – and how they could impact the sector – they should be constantly reassessing their strategies and developing the kind of agility required to adapt swiftly and decisively, to branch out in new directions and form appropriate alliances.

Key trends impacting the life sciences industry

- Demographics
- Environment
- Technology
- Social values and behaviours
- Ethical business and governance
- High growth markets

As KPMG UK's Head of Creative Thinking, Adam Bates helps both the firm and clients make the right strategic investments and develop new, innovative products and services.

3 *The future of employment: how susceptible are jobs to computerisation*, Frey CB and Osborne MA, Oxford Martin, Oxford University Engineering Sciences Department and the Oxford Martin Programme on the Impacts of Future Technology, 17 September 2013.

4 *Statistical Review of World Energy 2014, BP*, 2014.

5 *The Industries Plagued by the Most Uncertainty*, Harvard Business Review, 11 September 2014.

6 *Telstra ramps up health services division*, The Australian, 23 October 2014.

7 AliveCor website, http://store.alivecor.com, accessed 17 December 2014.

The deal landscape

Large, cross-border deals and asset swaps are set to continue, but tax inversions are likely to become less popular.

Rupert Hill

Managing Director, Greenhill & Co. International LLP

Transactions involving US pharma companies are being driven by three major forces. Firstly, the overwhelming power of the two big pharmacy benefit managers, Express Scripts/Medco and CVS, who are primarily responsible for processing and paying prescription drug claims, is driving down prices for both branded and generic products.

Secondly, wholesaler consolidation, particularly among generic and speciality players, is putting further pressure on prices in a market controlled by seven large pharmacies. And finally, the US's healthcare costs have reached breaking point, growing faster than national income, while tax revenues from the sector are falling due to tax inversions. At 18 percent of GDP the US spends more than eight times the world average on health, an unsustainable figure.

The mergers and acquisitions (M&A) market has been characterised by three, relatively novel types of deal. Therapeutic swaps are becoming more popular, in order to divest non-core businesses and build up others, with most big players reviewing their portfolios. One notable three-way deal involved Novartis, GlaxoSmithKline (GSK) and Eli Lilly. Such transactions have the added benefit of being less complex than a major M&A, although it can be tricky to value a part of a division.

The pharma M&A market has been characterised by therapeutic swaps, unwinding of conglomerate structures and tax inversions.

Some companies have chosen to unwind their conglomerate structure. Pfizer created considerable value for shareholders when selling its nutrition division to Nestlé in 2011, and spinning off its animal health business, Zoetis, in 2013, with a 62 percent share rise. Abbott's 2013 spinoff of its biopharma and diversified healthcare into AbbVie achieved similar success, with the new, slimmer version focused on medtech and pharma. Meanwhile the likes of Merck Co., Sanofi, GSK and Astra Zeneca are all exiting established therapeutic areas.

To avoid relatively high corporate tax rates, a number of companies are carrying out tax inversion deals, to relocate headquarters in lower tax countries via acquisitions. And, while the US government loses valuable tax income, the pharma company retains all its patent protection and other rights. A combination of the released cash and increased share price has arguably enabled the inverters to fund further acquisitions, such as Actavis' purchase of Forest and Valeant's bid for Allergan. Other sizeable inversions include Medtronic's purchase of Covidien and Abbvie's aborted attempt to buy Shire.

To date, these inverters have significantly outperformed the market, with impressive increases in share prices. However, this could be about to end, as inversions have recently come under scrutiny from the US Treasury and Internal Revenue Service (IRS), with subsequent changes, announced in September 2014, designed to reduce the associated tax benefits. In future, if the acquired company's shareholders hold less than 40 percent equity in the new entity, then the inverter cannot repatriate profits and must pay dividends out of US earnings only. Even reaching the minimum 20 percent threshold will be made more difficult, with more stringent interpretation of qualifying assets, and rules preventing the acquirer from 'shrinking' pre-acquisition.

Healthy multiples

Most of the large deals in recent times have tended to be either cross-border or transatlantic, with high multiples. Pfizer's ultimately unsuccessful pursuit of AstraZeneca would have meant paying over 15 times earnings, and a number of other deals reached multiples in the high teens or above, including Valeant's bid for Allergan, Actavis' acquisition of Forest, Novartis' purchase of GSK's oncology business and Bayer's acquisition of Merck's consumer care division. With some notable recent exceptions, however, transaction multiples have shown a slight downward trend in the past decade.

The variety in size of companies across the sector suggests that further M&As are likely. Indeed, were it not for the terminated deals between Pfizer and Astra Zeneca and Abbvie and Shire, the marketplace would look somewhat different.

Having been relatively close 10 years ago, the gap in value between fast moving consumer goods (FMCG) and pharma companies widened in favour of FMCG during the financial crisis, but more recently has converged again, in part impacted by the value gained from M&As. Indeed, with pharma companies building consumer health divisions, and firms like Reckitt outbidding pharmaceutical firms to buy several healthcare assets, the difference between such businesses is blurring slightly.

What does the future hold?

The ready availability of cash should ensure a continued flow of big deals, largely cross-border affairs between the US and Europe, rather than in emerging markets. Asset swaps are also expected to remain popular, with high target asset prices suggesting these kinds of deals have a strong potential to create value. However, swaps are more complex in nature and can arouse internal sensitivity, as a failed swap implies a lack of confidence in that business, which could impact both the future price and the overall value of the company.

Licensing and partnership agreements will provide a platform for further transactions, typically involving a smaller biotech and a major player, with the latter taking a Board seat early on, possibly licensing phase 2 products, with a potential acquisition at a later stage, pending a successful product approval. With most biotechs concentrated in the US, buyers will tend to come from domestic sources, as well as Japanese and European firms.

With overcrowding in certain sectors – such as oncology – consolidation may occur, either through joint ventures or M&As. Despite the pressure from the US government, tax inversions are likely to remain attractive, although not to the same degree as previously. Steris' 1 billion dollar (US$) takeover of Synergy Health shows that there is life in this type of deal.

Shareholder activism is a continuing force, particularly in the US, and could lead to transactions. At the time of writing, biotechnology giant Amgen was being urged to break in two by hedge fund shareholder Third Point, to streamline R&D and reform its cost structure[8].

Looking further ahead, big pharma will most probably retain its three-pronged market structure of pure-play, research driven companies like Roche, diversified groups such as GSK, and conglomerates. Emerging markets, on the other hand should change dramatically. Currently, branded drugs, generics and consumer products tend to be distributed and sold through the same channels, reducing the need to unbundle different divisions. Maturity may bring more defined market structures that call for more specialised approaches, opening up opportunities for deals, as the global players divide into either innovators or generic providers.

Another trend to look out for is the rise of therapeutic 'champions' that concentrate on a smaller number of disease areas. Astra Zeneca is one such example of a company that simply is not big enough to do everything.

Rupert Hill was previously Head of Healthcare for EMEA and Asia-Pacific at Bank of America Merrill Lynch, advising on some of the largest healthcare transactions in Europe and the emerging markets.

8 *Amgen: $100 Billion Activist Target,* Wall Street Journal, 21 Oct 2014

Big pharma will most probably retain its three-pronged market structure of pure-play, research driven companies like Roche, diversified groups such as GSK, and conglomerates.

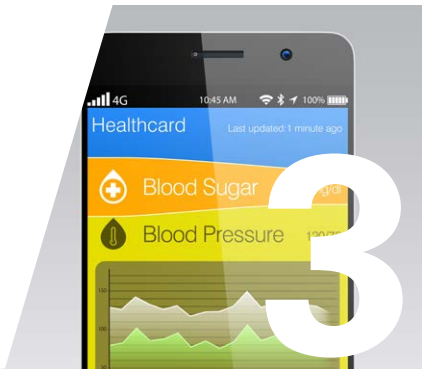
Conclusion: Four key future imperatives

Turn invention into innovation

The life sciences sector should strive to create relationships with universities based upon mutual trust, where academics maintain a focus on commercially viable research, and pharma companies encourage creativity and acknowledge and reward success.

Contribute to fast, safe regulation

Several regulatory authorities are speeding up the approval process through adaptive licensing – a strategy that will ideally be taken up worldwide. By working more closely with regulators and being completely transparent about research data, life sciences companies can help this acceleration, as well as learning sooner about compounds that are unlikely to be approved, saving time and research dollars.



Address new competition

With new entrants from industries such as technology and food, traditional pharma companies' hegemony is under severe threat. The main players must continually assess trends, adapt their business models and move decisively to ally with promising start-ups.

Evaluate future deal flows

Although the current trends of asset swaps, large cross-border transactions and, to a lesser extent, inversions, are set to continue, industry players should keep a close eye on emerging markets. In fast-maturing BRICs, pharma is likely to become more specialised, offering opportunities to pick off branded drugs, generics and consumer divisions of existing players.

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