



feature



The changing model of big pharma: impact of key trends

Ajay Gautam, ajay.gautam@astrazeneca.com and Xiaogang Pan

Recent years have seen exciting breakthroughs in biomedical sciences that are producing truly novel therapeutics for unmet patient needs. However, the pharmaceutical industry is also facing significant barriers in the form of pricing and reimbursement, continued patent expirations and challenging market dynamics. In this article, we have analyzed data from the 1995–2015 period, on key aspects such as revenue distribution, research units, portfolio mix and emerging markets to identify four key trends that help to understand the change in strategic focus, realignment of R&D footprint, the shift from primary care toward specialty drugs and biologics and the growth of emerging markets as major revenue drivers for big pharma.

Introduction

Big pharma has seen a significant change in operating model and footprint over the past couple of decades. Several studies have reviewed the industry's declining productivity challenges [1,2], the transitioning of commercial models [3,4] and the growth of emerging markets as key revenue contributors [5]. In this article, we have reviewed the key trends that have impacted and transformed the big pharma companies over the past 20 years. The current big pharma model is transitioning to that of a lean, focused company with a research footprint within key innovation bioclusters and a growing revenue stream from specialty products and biologics and emerging markets. By contrast, the 1990s and early 2000s model was that of a large, diversified company with R&D footprints in multiple global hubs, and primary care businesses driving a large portion of revenues with minimal contribution from the emerging economies.

We collected data across different parameters such as: revenue percentage from biologics, specialty and primary care portfolios; mergers and acquisitions; regional growth rates; research footprint and sites globally; revenue split between the established (USA, Europe and Canada) and the emerging (Asia, Latin America, Russia, Middle East and Africa) markets; among others. We used public and proprietary sources such as IMS Health (<http://www.imshealth.com/>), company annual filings, industry reports and press releases for the top 12 innovation-driven pharmaceutical companies. The data were analyzed over two contiguous ten-year time periods of 1995–2005 and 2005–2015 to understand the changes and any trends over the past two decades. We chose a ten-year period for the data analysis because that is a relevant timeline for a full R&D cycle for the pharmaceutical industry. Our data review revealed four trends that we have classified as:

- massive to lean;
- hubs to hotspots;
- primary to specialty;
- West to East.

Each of these trends and the impact on the big pharma operating model is discussed in more detail below.

The key trends impacting the big pharma model

Massive to lean

The 1995–2005 period was marked with intense mergers and acquisition activity, starting with the mergers between Astra and Zeneca, Ciba-Geigy and Sandoz, Pfizer and Warner Lambert, Sanofi and Aventis, and Glaxo and SmithKline, culminating with the Pfizer-Pharmacia merger in 2003 (Table 1). A push for the 'bigger is better' model resulted in bloated operations across the globe – large R&D hubs, armies of sales reps, multiple manufacturing sites, often confusing

TABLE 1

Massive-to-lean strategy.

Expanding organizations		Company		Leaner, focused organizations
Astra and Zeneca merger	1999	AstraZeneca	2014	Narrow therapy areas from five to three
Acquired MedImmune	2007			
Merged with Schering	2006	Bayer	2014	Divested material science and specialty chemicals businesses
Acquired biologics expertise through Medarex	2009	Bristol-Myers Squibb	2008 2009 2014	Divestiture of medical imaging and wound care businesses Spin-off of nutrition business Mead-Johnson Divested diabetes business to AstraZeneca; focus on three therapy areas
Merger of GlaxoWellcome and SmithKline Beecham	2000	GlaxoSmithKline	2014	Swapped oncology for consumer health and vaccines with Novartis
Acquired Schering-Plough	2009	Merck	2014	Divested consumer health to Bayer
Merger of Ceiba-Geigy and Sandoz	1996	Novartis	2014	Divest animal health to Eli Lilly; swapped vaccines and consumer health for oncology with GSK
Acquired Warner Lambert	2000	Pfizer	2006	Divested consumer health to JNJ
Acquired Pharmacia	2003		2012	Spin-out animal health unit (Zoetis)
Acquired Wyeth	2009		2012 2015	Divested nutrition business to Nestle Acquired Hospira for biosimilars On track to split into three businesses: innovative pharma; established products; oncology/vaccines
Acquired biologics expertise through Genentech	2009	Roche		
Merger of Synthelabo and Sanofi	1999	Sanofi	2011	Acquired biologics expertise through Genzyme
Merger of Aventis and Sanofi	2004			
		Abbott	2013	Split into two companies: Abbott for diversified healthcare products and AbbVie for innovative pharma business
		AbbVie	2015	Acquired Pharmacyclics for oncology business
		Baxter	2015	Divested innovative pharma business as Baxalta

and matrixed governance layers – all further compounded by a lack of cultural integration of the merged companies. A consolidation in the industry was justified by economies of scale, diversified portfolios and businesses across the healthcare spectrum as an antidote to looming patent cliffs, and to overcome declining R&D productivity.

By contrast, since the late 2000s, big pharma has started to embrace a 'leaner and focused' model by divesting non-core assets and focusing on their areas of strengths (Table 1). Consider some recent examples: Abbott split into two parts [an innovative business (AbbVie) and a diversified healthcare company (Abbott)]; GSK and Novartis swapped their oncology, consumer health and vaccines business to create focused organizations with GSK increasing the focus on consumer health and vaccines and Novartis on oncology; AstraZeneca narrowed the focus to three core therapy areas of oncology, cardiovascular-metabolism and respiratory, inflammation and autoimmune disease, and in the process divested infectious disease and created a semi-autonomous, virtual unit for neuroscience; and Bristol Myers-Squibb (probably the most transformative) divested large parts of the organization (medical devices, nutrition, consumer

health, multiple therapy areas) to position as a specialty company in oncology, cardiology and virology.

This is not to suggest that the 2005–2015 period has not witnessed significant acquisitions – Roche and Genentech for biologics in 2009 as well as Sanofi and Genzyme for rare diseases and biologics in 2011 are such cases, as are Pfizer's acquisition of Wyeth for biologics and of Hospira for entering biosimilar business and AbbVie's acquisition of Pharmacyclics for oncology business and to offset reliance on Humira[®]. But acquisitions during this period were largely driven by strategic rationale and to build complementary capabilities rather than a desire to be 'massive'. Of course, over the past couple of years, acquisitions driven by tax inversions have also been popular, such as Valeant's multiple acquisitions, Actavis-Watson-Allergan mergers and Mylan acquisition of Abbott's European generics business, among others. But these are as much, if not more, a result of financial engineering as they are of pure strategic drivers, as well as a desire by smaller players to gain scale and geographic reach. It is an interesting dichotomy where the large players are seeking to be focused and leaner through divesting, whereas smaller players are following the 'bigger is better'

playbook of big pharma from the 1990s to become massive.

Hubs to hotspots

The wave of mega acquisitions was largely triggered by declining R&D productivity. The economies of scale were used as one justification for integrating the dispersed research units and therapy areas across the merged companies. An unintended consequence was creation of multiple research hubs across the globe: Pfizer's multiple units in the USA and UK; AstraZeneca's research sites in Sweden, USA, Canada and UK; Roche's US and Switzerland sites; Novartis sites in the UK, USA and Switzerland; GSK's US and UK units, among others (Fig. 1). These sites created self-contained silos that were used as research units for high-throughput technologies in an attempt to throw more money and hands at solving scientific challenges – a 'more shots on goals' strategy.

The past decade, by contrast, was marked with a desire to locate within bioscience hotspots – the innovation clusters such as Boston, San Francisco, San Diego, Cambridge and London in the UK, Shanghai – which are increasingly the key centers for producing breakthrough science. Localizing their research units in these hotspots

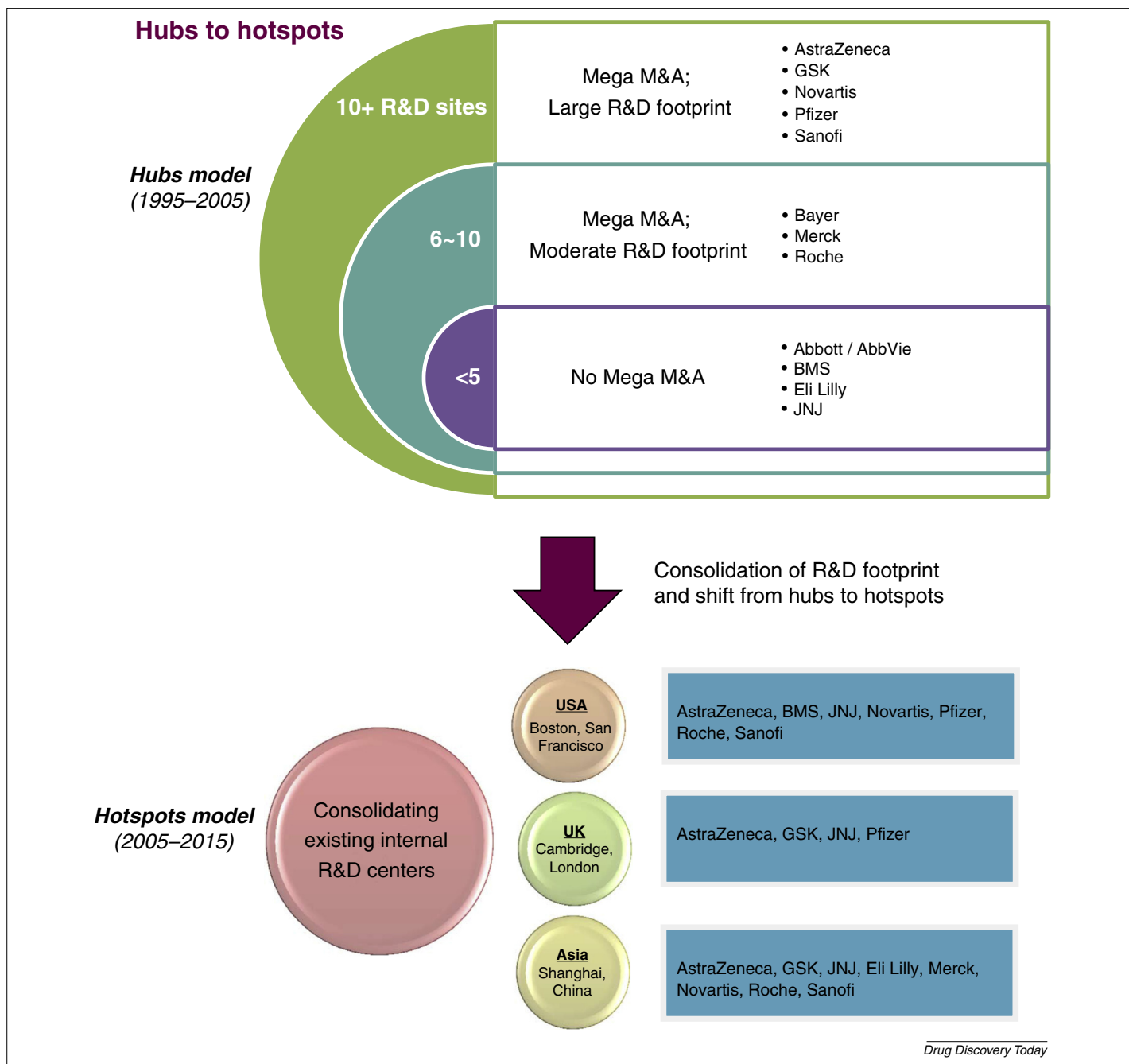


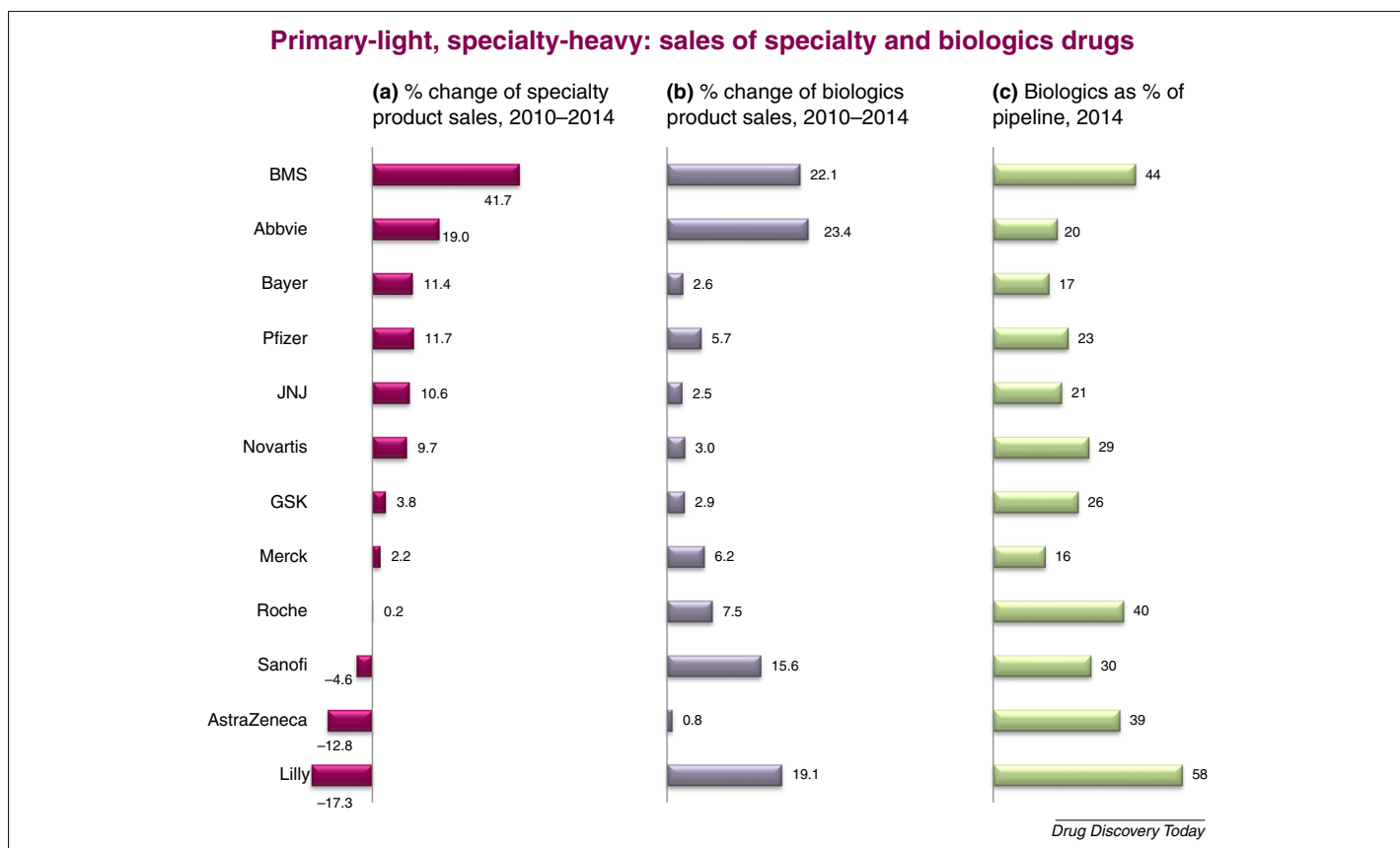
FIGURE 1

The data for our big pharma cohort reveals a shrinking R&D footprint and shift from large hubs to innovation hotspots. Qualitative and quantitative data are shown. Source: industry reports, company filings and press releases.

enables big pharma scientists to work closely with external researchers and clinicians in progressing their drug pipeline, a much more open and collaborative model versus the ‘not invented here’ syndrome of the hubs model. Novartis was probably a pioneer in this trend, relocating its research headquarters to Cambridge, Massachusetts, in the early 2000s and several of the big pharma companies followed suit. Roche closed its Nutley site in New Jersey and moved to New York City, another innovation hotspot, as well as having consolidated US research operations in

South San Francisco. In 2013, AstraZeneca announced that it would move its research headquarters from Alderley Park, UK, to Cambridge, UK, which is a rich scientific and entrepreneurial ecosystem. In 2013, JNJ established its innovation centers in key hotspots globally: San Francisco, Boston, London and Shanghai, and Merck and BMS are also implementing this approach. There are still large hubs: the Roche and Novartis sites in Basel, Switzerland, the Lilly site in Indianapolis and Merck in New Jersey, to name a few, but the trend toward hotspots is clear.

Over the past decade, big pharma’s R&D organizations have also experienced a paradigm shift by experimenting more entrepreneurial internal biotech units. Two such examples are GSK’s Discovery Performance Unit and AstraZeneca’s Virtual Neuroscience Unit. Further, the research units have increasingly used CROs and CMOs for strategic drug discovery alliances, such as Pfizer’s strategic partnerships with Parexel, Ikon and PPD, and AstraZeneca’s partnerships with Wuxi AppTec and Pharmaron, rather than perform such functions within their hitherto

**FIGURE 2**

Data showing specialty and biologics products growth for big pharma cohort in our study during the 2010–2014 period. Majority of the companies saw an increase in specialty pharmaceuticals (a) and biologics (b) sales as proportion of portfolio during the period. The biologics proportion of the pipelines of various companies also reveals 20–60% of the portfolio comprised such molecules (c). Source: IMS Health Analytics. Specialty and biologics sales and pipeline distribution are as per IMS Health definitions and data.

hubs. Finally, localizing within the global hot-spots has also allowed big pharma research organizations to broaden the access of external innovation through targeted alliances and collaborations with the academic institutions and biotechs in these innovation ecosystems.

Primary-light, specialty-heavy

The 1995–2005 period was the quintessential blockbuster drugs era for big pharma, so much so that two of the largest mergers in the industry were primarily driven by single blockbusters: Lipitor[®] in case of Pfizer-Warner Lambert and Celebrex[®] in case of Pfizer-Pharmacia. Some of the biggest-selling drugs in the industry's history – Lipitor[®], Plavix[®], Nexium[®], Abilify[®], Seroquel[®], Diovan[®], Crestor[®], among others – were launched during this period. Further, most of the top-selling drugs during the 1995–2005 period were primary care, small-molecule therapies. During this period, the primary care therapy areas accounted for ~80% of revenues for most of the big pharma portfolios.

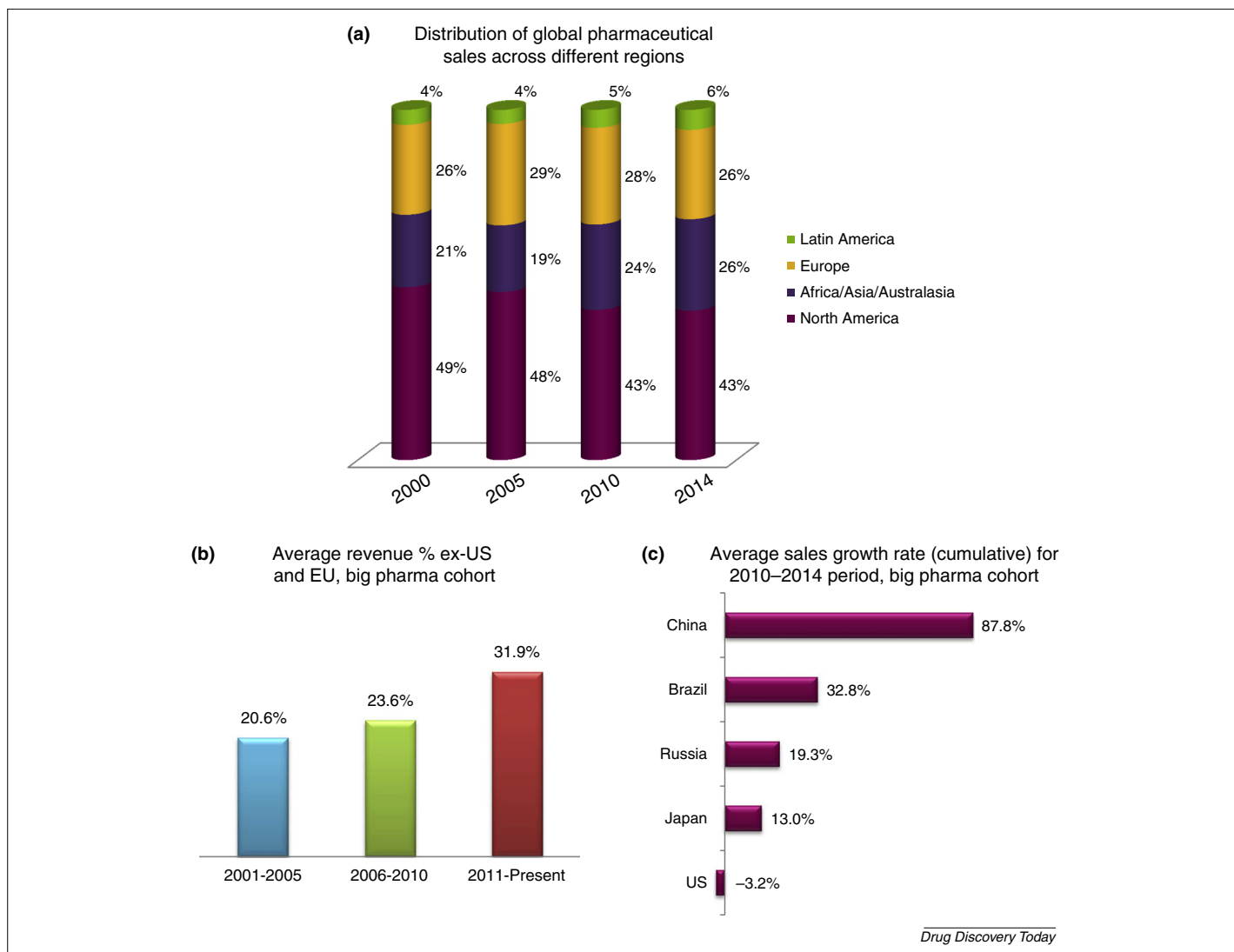
Over the past decade, however, big pharma has been shifting away from developing primary

care and small-molecule medicines, and progressively tailoring their pipelines to specialty medicines and biologics targeted for high unmet medical needs. The trend is driven by several factors such as: better understanding of the underlying disease biology to develop targeted medicines; science and technology innovation for biologics; personalized medicines and companion diagnostics; favorable regulatory framework and development timelines for such medicines; and pricing and reimbursement.

Big pharma largely missed the biologics wave early on, and caught up to the antibody, protein and cell therapies during the 2005–2015 period primarily through targeted acquisitions such as Roche-Genentech, Sanofi-Genzyme, Lilly-Imclone, BMS-Medarex, AstraZeneca-MedImmune and Pfizer-Wyeth. By 2015 this effort started to bear fruits and most of the big pharma portfolios now have an even distribution between specialty and primary care units, as well as the development pipelines that are evenly distributed between small- and large-molecule drug candidates. In 2014, for example, primary care medicines only accounted for approximately

one-quarter of new FDA-approved new molecular entities (NMEs), as per consulting firm PwC's Health Research Institute study.

Over the past couple of decades, most big pharma companies have also observed increased revenues from the specialty medicines and biologics portion of their portfolios, with several big pharma companies showing a greater than 10% absolute percentage increase for proportion of specialty products and biologics during the 2010–2014 period, as per IMS Health data (Fig. 2). Although AstraZeneca, Lilly and Merck observed a drop of percentage sales of specialty medicines over the past five years, it was mainly caused by patent expiration of the top-selling medicines, such as Zyprexa[®] for Eli Lilly, Taxotere[®] for Sanofi and Seroquel[®] for AstraZeneca. The development pipelines have clearly shown a ramp-up and increased focus on specialty and biologic medicines as part of overall company portfolios as well, with AstraZeneca's ~40% of clinical stage molecules being biologics, and the split being ~30% and ~58% biologics for Sanofi and Eli Lilly, respectively, as per IMS Health data.

**FIGURE 3**

(a) West to East: global pharmaceutical sales by region. Data showing global pharmaceutical sales in constant dollars. During the 2000–2014 period, Asia-Pacific/Africa region saw a 5%+ increase in share of global pharmaceutical sales. Latin America increased ~2% share during the same period, whereas the North America saw a decline of 6% and Europe had essentially a flat-to-modest decline. Source: IMS Health World Review Analysis. Regional sales distributions are as per IMS Health definitions and data. **(b,c)** West to East: big pharma sales and growth rate outside the USA and EU. **(b)** Data showing average global pharmaceutical sales in constant dollars. During the 2000–2014 period, the big pharma companies in our dataset saw sales proportion from Asia Pacific and emerging markets increase by ~10% in absolute terms. **(c)** Data showing average cumulative sales growth during the 2010–2014 period in key markets. Majority of the sales growth outside the USA, EU and Japan came from key markets such as China, Brazil and Russia. The average sales growth (cumulative) for the big pharma cohort in our study was ~88% in China during the 2010–2014 period, whereas US sales declined by ~3%. Source: Company Annual Reports and IMS Health Analytics. The regional sales distribution is as per IMS Health definition and data.

West to East

Whereas North America and Europe were the leading major markets for the global pharmaceutical industry in the 1995–2005 period, the emerging markets of Asia, Latin America, Russia, Middle-East and Africa continue to spearhead revenue growth over the recent decade owing to strong demand and economic fundamentals (Fig. 3a). During the 1995–2005 period none of the big pharma companies in our study had more than 20% revenues derived from the emerging markets. By contrast, during the following decade of 2005–2015 most big pharma companies grew

their portfolios to comprise at least 25% of the total revenues from the Asia Pacific and emerging markets, with the figure as high as ~35% for Sanofi. In 2014, for example, AstraZeneca sales from these markets accounted for ~US\$6 billion in revenues and emerging markets accounted for ~US\$14 billion sales for Sanofi and ~US\$10 billion for GSK, as per company annual filings. China has largely been the driver for such stupendous growth, but Brazil and Russia have contributed significantly as well (Fig. 3b,c).

There is, however, a bifurcation in this West to East dynamics, depending on the diversification

of company portfolios between primary versus specialty-heavy businesses. Firms such as AstraZeneca, GSK, Pfizer and Merck saw emerging market businesses grow significantly as a proportion of global revenues because of the patent expiry of products in the USA, Canada and EU during the 2005–2015 period and a concomitant growth of their largely primary care business in the emerging markets. Other firms with heavier biologics focus such as Roche, JNJ and Amgen did not see as much increase in emerging markets revenue ratios because they did not face as severe a patent cliff in North

America and Europe as their counterparts that had primary-care-focused portfolios.

Not just commercially, the emerging markets, specifically China, have also seen a large increase in innovation capabilities [6] over the past decade. As the world's second-largest pharmaceutical market, backed by significant government and private capital, growing talent pool of experienced Western-trained returnees and home-grown professionals and an evolving life science ecosystem [7], China is rapidly progressing as a hotspot for global innovation. Most big pharma companies have established their research units in China including AstraZeneca, Eli Lilly, GSK, JNJ, Novartis, Roche and Sanofi, all in Shanghai, and Merck, Novo Nordisk and Bayer in Beijing. Amgen is the latest to announce establishing a research unit at the ShanghaiTech University in 2014.

Concluding remarks: what might 2015–2025 look like?

The demand for new therapies will continue to see steady growth, a favorable trend for the long-term industry dynamics [8]. However, there are significant challenges for the industry such as: continued patent expiration; regulatory hurdles; access, pricing and reimbursement; and R&D productivity. Big pharma companies have been revamping their strategies to remain competitive in this new business environment. The major players are rapidly aligning into two distinct camps: (i) a diversified business, such as Abbott, Bayer, Eli Lilly, GSK, JNJ, Merck and Sanofi, that has a mix of diagnostics, generics, medical devices, innovative drugs, consumer health and animal health businesses under a single umbrella organization; and (ii) pure play biopharma companies such as AbbVie, AstraZeneca, Bristol-Myers Squibb, Novartis, Pfizer and Roche, which are focused primarily on innovative drugs (we have assumed Novartis and Pfizer to be transitioning toward pure play biopharma based on their strategic plans to divest or split non-core and adjacent businesses). Within the two camps, the companies have adopted diverse strategies to evolve their businesses: the pursuit of specialty medicine and biologics; asset-swapping to focus on leadership businesses and exit non-aligned portfolios; geographic expansion and regional consolidation; R&D restructuring; and bolt-on acquisitions and partnership. We envision big pharma's business model will continue to evolve over the next decade, with each of the four key trends identified here continuing to shape the industry.

A key challenge over the coming decade will be affordability – the new and exciting

breakthroughs in immuno-oncology [9], respiratory, stem cells, gene therapy and technology platforms such as clustered regularly interspaced short palindromic repeats (CRISPR) and RNA therapeutics [10,11] will pave way for effective, novel drugs. However, these therapies continue to be expensive and new pricing and reimbursement models are needed to make them more affordable for patients. Providing sustainable access to healthcare will be a significant global challenge for all stakeholders – government, payers and healthcare companies – and this is, and will continue to be, the case for the emerging economies where healthcare systems are largely out-of-pocket. These emerging markets, however, account for almost one-quarter-to-one-half of the revenues for big pharma. How the companies price these products and broaden the access of medicines is a key challenge for the next decade. New models such as coverage assistance, tiered pricing, performance-based models, among others, will need to be broadly explored and implemented. The partnership of Gilead with Indian generic firms to provide affordable access to sofosbuvir (marketed under the brand name Solvadi[®] for hepatitis C disease) in the Indian subcontinent, and that of Roche with private insurers in China for access to biologics drugs, are examples of such models being tested.

The convergence of IT and healthcare is another area that would impact the big pharma model over the coming years. Big data and mobile health are starting to transform healthcare and diagnostics in a significant way, with new players such as Apple and Google acting as increasingly disruptive catalysts. Medicines paired with companion diagnostics have been a successful strategy to gain market access, and firms such as AstraZeneca, Roche, Novartis and Sanofi are progressing as much as 60–80% of their clinical portfolios with companion diagnostics. In the personalized and precision medicines era, this strategy will probably translate into medicines accompanied with apps or wearable devices that help patients monitor key parameters and manage their diseases. How big pharma adapts to this 'beyond-the-pill' model will be an interesting development during the 2015–2025 period.

Finally, there is likely to be a new breed of companies that will start to emerge from countries such as China, India, Korea and Brazil to challenge the long-held leadership of US and European companies. The top 10 largest companies globally across all industries in 1995–2005 were all from the USA or Europe; today at least half of the top 10 is from emerging markets,

primarily China [12]. The pharmaceutical industry, given the long development timelines and regulatory hurdles, is still dominated by US and European players. There are, however, aspirations from companies such as Sun Pharma from India, Teva from Israel, Celltrion and Hanmi from Korea, Hengrui Pharma and Fosun Pharma from China, EMS Pharma from Brazil, among others, to be leading global players. It is unlikely that any of these firms will become global innovators imminently, but by 2025 some of these emerging markets companies could be in a position to compete with global leaders such as Pfizer, Novartis, AstraZeneca and Merck.

References

- Paul, S.M. *et al.* (2010) How to improve R&D productivity: the pharmaceutical industry's grand challenge. *Nat. Rev. Drug Discov.* 9, 203–214
- Khanna, I. (2012) Drug discovery in pharmaceutical industry: productivity challenges and trends. *Drug Discov. Today* 17, 1088–1102
- Kessel, M. (2011) The problems with today's pharmaceutical business – an outsider's view. *Nat. Biotechnol.* 29, 27–33
- IMS Health Report (2009) Understanding new commercial models. Available at: http://www.imshealth.com/deployedfiles/imshealth/Global/Content/StaticFile/Understanding_New_Commercial_Models.pdf
- Looney, W. (2010) Strategies for emerging markets: seven keys to the kingdom. *Pharma. Executive* 30, 8
- Gautam, A. and Yang, S. (2014) A framework for biomedical innovation in emerging markets. *Nat. Rev. Drug Discov.* 13, 646–647
- Gautam, A. (2015) Evolution of Chinese bioclusters as a framework for investment policies in emerging markets. *Nat. Rev. Drug Discov.* 14, 8
- IMS Health (2014) Global outlook for medicines through 2018. Available at: <http://www.imshealth.com/portal/site/imshealth/menuitem.762a961826aad98f53c753c71ad8c22a/?vgnextoid=6011f106fe3c9410VgnVCM10000076192ca2RCRD>
- Crusz, S.M. and Balkwill, F.R. (2015) Inflammation and cancer: advances and new agents. *Nat. Rev. Clin. Oncol.* 12, 584–596
- Sander, J.D. and Joung, J.K. (2014) CRISPR-Cas systems for editing, regulating and targeting genomes. *Nat. Biotechnol.* 32, 347–355
- Sahin, U. *et al.* (2014) mRNA-based therapeutics – developing a new class of drugs. *Nat. Rev. Drug Discov.* 13, 759–780
- Forbes Global 2000 Companies List (2015) The world's biggest public companies. Available at: <http://www.forbes.com/global2000/list/>

Ajay Gautam*
Xiaogang Pan

AsiaPac & Emerging Markets, IMED Biotech Unit, AstraZeneca, 199 Liangjing Road, Zhangjiang Hi-Tech Park, Shanghai 201203, China

*Corresponding author: