Catalyst

Health policy initiatives and funding issues drive rapid changes.

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EXECUTIVE SUMMARY

Emerging markets are attractive targets that present unique challenges

- Worth an aggregate of some $200bn and, in most cases, still growing at double-digit rates, the pharmaceutical markets in the BRIC/MIST countries (Brazil, Russia, India, China, Mexico, Indonesia, South Korea, and Turkey) represent an attractive target for the industry. Large, traditionally underserved patient populations mean unmet demand for medicines is considerable, but manufacturers attempting to unlock that potential face some tough challenges. Most BRIC/MIST countries are still predominantly self-pay pharmaceutical markets, and private sector demand for original brands is limited. Where the provision of government-subsidized medicines is available it is dominated by low-cost generics, and modest budgets demand a conservative approach by regulators to the inclusion of original brands on public formularies. Deficient health infrastructures, a dearth of specialist prescribing expertise, and, in some countries, poorly managed procurement and distribution systems pose additional barriers to institutional market access.

- For originators, success in these markets demands flexibility – and not just where pricing is concerned. The ability to engage effectively (and innovatively) with a broad range of stakeholders, and to accept that business models must be adapted to fit the demands of individual markets, are both vital prerequisites of winning BRIC/MIST strategies. These demands are changing more rapidly than ever, reflecting developments that will affect strategies at all stages of the commercial lifecycle, from obtaining protection for their intellectual property, through the development and registration of new drugs, to the pricing, promotion, and prescription of original brands.

Intellectual property protection is improving, but remains problematic

- World Trade Organization commitments and pressure exerted by major trading partners are driving gradual improvements in most BRIC/MIST intellectual property protection frameworks. Ineffective patent protection and limited exclusivity still pose significant problems, however, while concerns surrounding the availability of affordable drugs are fueling a pushback against the introduction of stronger intellectual property protection frameworks in countries such as India and Indonesia. Compulsory licensing of patented medicines remains a threat in both of these countries, and has been discussed recently by regulators in Russia.

Regulatory reforms solve some problems – but create others

- Local trial requirements have been relaxed for orphan drugs and, in some countries, other new products targeting serious, life-threatening diseases. Expedited clinical trial approval procedures have also been established in Brazil, Mexico, Russia, and China as part of a drive to shorten drug lag times. Hopes that local trial waivers might be issued more widely in Russia have been dashed, however, while regulators in India are wrestling to mitigate the impact of punitive new liability and compensation rules on clinical research activity there.

- Registration regimes in several BRIC/MIST markets have been overhauled or are being reformed in a bid to reduce drug approval times. Medicines agency resources are being beefed up, systems fine-
tuned, review target times trimmed, and expedited review pathways established or expanded. The most dramatic improvements have been witnessed in Mexico, where regulators now recognize marketing authorizations issued in the US, EU, and several other developed markets. Elsewhere, review target times have been reduced in Russia, while new marketing authorization rules designed to help clear a massive application backlog are being rolled out in China. Not all developments are positive for originators, however, with regulations in some BRIC/MIST markets continuing to favor domestic manufacturers. In Indonesia, foreign companies are still unable to obtain marketing authorizations unless they establish local manufacturing capabilities or employ the services of a domestic partner. In China, meanwhile, new drug classification criteria appear to preclude access to fast track reviews for products that have already been approved or marketed in other countries.

**Cost-containment is driving pricing and reimbursement policy**

- Where governments have begun to foot a larger share of national drug spending bills, a more interventionist approach to pricing policy is generally being pursued. Private sector prices remain free from regulatory control in Mexico and Indonesia, but are being regulated more widely in India, and remain firmly in the grip of government controls in Brazil. Institutional market prices are under particular pressure, with price caps, compulsory discounts, and increasingly aggressive tendering policies all being used to limit procurement costs. In Mexico, the Social Security Institute (Instituto Mexicano del Seguro Social) is administering bulk tenders on behalf of a growing number of public purchasing agencies, while in China, provincial procurement strategies have continued to drive down procurement costs.

- For innovative new drugs, price is often the sole criterion determining access to public formularies – even where more rounded reviews (including the use of health technology assessments in countries such as South Korea and Brazil) are supposedly undertaken. Additions to the formularies managed by Mexico’s two biggest public payers have dried up almost completely, while in Brazil, fewer than one in five applications from manufacturers for inclusion on public formularies have been approved over the past five years. In China, the national reimbursement list has not been updated since 2009, and provincial formulary listings have become the key target for originators. In addition, risk- and cost-sharing agreements have begun to emerge as a feature of several BRIC/MIST reimbursement markets, and will play a growing role in the future.

**Distribution chain dynamics are changing**

- Competitive pressure and the imposition of tougher regulations are driving the consolidation of BRIC/MIST drug distribution markets. In countries where multiples control substantial shares of the retail market, and where vertically integrated businesses are a feature of the distribution chain, this will pose challenges for manufacturers attempting to shift their brands through retail pharmacies. In large, geographically complex markets such as China and India, it will represent a more welcome development, driving down costs and enabling manufacturers to maintain better control over their products throughout the distribution chain.

**Prescribing and promotion are subject to growing scrutiny**
- Prescribers are beginning to come under closer scrutiny in the BRIC/MIST markets, especially where government-funded reimbursement has been made available more widely. Monitoring and control systems are tightest in South Korea, but efforts to encourage or mandate more cost-effective prescribing are being stepped up elsewhere. The ability of regulators to police prescribing effectively remains limited in some countries, however.

- Relationships between physicians and manufacturers are also under the spotlight, following revelations surrounding the use of unethical methods to drive the prescription and sale of branded drugs in several BRIC/MIST markets. In China, this has triggered the introduction of new rules governing the conduct of both providers and suppliers, with manufacturers found guilty of corrupt practices facing exclusion from provincial or even national tender markets. In Turkey, meanwhile, mandatory certification of sales representatives is being introduced. To avoid falling foul of tougher new sanctions, manufacturers will be forced to review and strengthen existing compliance programs.
THE BRIC/MIST MARKETS

Subsequently a UK government minister, but then head of asset management at US investment bank Goldman Sachs, Jim O'Neill is the man who in 2001 coined the BRICs acronym. He used it to aggregate four emerging markets – Brazil, Russia, India, and China – which, he predicted, would together outrank the six biggest Western economies before the middle of this century (Goldman Sachs, 2001).

Later, O'Neill identified a list of other developing countries with substantial economic growth potential, dubbing them the Next-11. In 2012, he singled out four countries from that list which he said possessed the capacity to act as particularly strong contributors to future global economic growth. The four were Mexico, Indonesia, South Korea, and Turkey, triggering the inevitable birth of a new acronym: the MIST economies (The Guardian, 2011).

While some question the merits of grouping together these geographically, culturally, and politically diverse countries, their treatment as a collection of markets with significant future potential for the pharmaceutical industry makes particular appeal. All eight are home to sizable populations that have traditionally been poorly served in terms of healthcare provision. Governments in all eight countries have sought (or are actively seeking) to broaden access to healthcare in general, and to pharmaceuticals in particular. Coupled with rising patient incomes, this is driving a rapid, sustained increase in demand for medicines.

With growth in its traditional core markets slowing, the global pharmaceutical industry has jumped enthusiastically aboard the emerging market bandwagon, investing heavily in most BRIC/MIST countries. Those investments began to pay off and, for a time, strong growth in emerging markets helped to offset more modest results elsewhere. But having ridden out the early impact of the global recession, emerging market economies have begun to slow. Some – notably Brazil and Russia – are now in serious trouble.

This tougher economic climate has potentially major implications for healthcare systems in some BRIC/MIST markets, and for stakeholders including the pharmaceutical industry. It has heaped pressure on government healthcare budgets, putting reform plans at risk, and has begun to undermine patient purchasing power in countries where patients foot the majority of national drug spending bills.

Deteriorating economic conditions have triggered the imposition of more stringent pharmaceutical cost-containment mechanisms, and are forcing some patients to trade down from original brands to cheaper generics or branded copies. The impact of slower economic growth may be greater in the longer term if it forces the postponement or re-evaluation of expansive healthcare reform plans. And while patient incomes will recover when economies begin to rebound, measures designed to curb drug spending will remain in place. These will pose a significant challenge for originators pursuing further inroads into the BRIC/MIST markets.

**BRIC/MIST markets share several common characteristics**
Diverse in many other ways, the BRIC/MIST markets share some important characteristics where healthcare provision and pharmaceutical consumption are concerned. While China and India are in a league of their own, the other six countries also possess substantial patient populations. Their economies may have expanded rapidly over the past decade, but most have done so from a relatively modest base. Per capita incomes are either modest or low. Coupled with geographic challenges and the often inadequate nature of public health infrastructures, this has traditionally undermined the ability of many poor patients to access medical care.

Although most BRIC/MIST countries still spend a modest proportion of their respective gross domestic product (GDP) on healthcare, government contributions to national expenditure in the sector have risen, reflecting commitments to investment in the public health infrastructure and the provision of subsidized basic healthcare. Most have either achieved universal basic provision in the relatively recent past, or are still actively pursuing that target. Where basic coverage is complete, improvements in the range and quality of subsidized health benefits are being pursued.

Rapid economic expansion has driven up incomes. Coupled with the expansion of health infrastructures and the introduction of subsidized basic provision, this has triggered a surge in demand for healthcare. Improvements in provision have boosted life expectancy, but urbanization and dietary/lifestyle changes have seen chronic non-communicable diseases (NCDs) emerge as potent new threats to the health status of patient populations.

Change in many of these areas has been witnessed at dramatic rates, creating dynamic, sometimes highly volatile pharmaceutical markets in which, rather than setting the agenda, regulators have been struggling to catch up with events. The reactive nature of regulatory policy will continue to pose problems for the pharmaceutical industry, which will be forced to deal with new rules, sometimes introduced at short notice, that have the potential to transform the market environment.

In some BRIC/MIST markets, the picture will be complicated further by frequent, sometimes major discrepancies between the content of the regulations and the extent to which they are enforced or complied with on the ground. This often reflects the inability of regulators to police laws effectively, but on occasion amounts to a tacit acknowledgment that new rules are unworkable in practice, and will be widely ignored. The ability to gauge accurately the degree of intent behind individual regulations can be vital for companies operating in markets where new rules are being ratified on a regular basis.
### Table 1: Key constraints and drivers of market access in BRIC/MIST markets

<table>
<thead>
<tr>
<th>Area</th>
<th>Constraints</th>
<th>Drivers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intellectual property protection</td>
<td>- Restrictive patentability criteria</td>
<td>- Patent linkage</td>
</tr>
<tr>
<td></td>
<td>- Ineffective patent protection</td>
<td>- Patent term restoration</td>
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<td></td>
<td>- Compulsory licensing</td>
<td>- Effective mechanisms for the timely resolution of patent disputes</td>
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<tr>
<td></td>
<td>- Absence or abuse of data protection provisions</td>
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<tr>
<td>Clinical development</td>
<td>- Lengthy trial approval procedures</td>
<td>- Reform of trial approval procedures</td>
</tr>
<tr>
<td></td>
<td>- Substantive local trial requirements</td>
<td>- Government support for trial networks</td>
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<td></td>
<td>- Local trial waivers</td>
<td></td>
</tr>
<tr>
<td>Registration</td>
<td>- Under-resourced medicines agencies</td>
<td>- Medicines agency recruitment drives</td>
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<td></td>
<td>- GMP certification</td>
<td>- Mutual recognition of GMP certification</td>
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<td></td>
<td>- Bureaucratic, non-transparent review procedures</td>
<td>- Fast track approval pathways</td>
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<tr>
<td>Pricing</td>
<td>- Restrictive controls on launch prices</td>
<td>- Premium prices for truly innovative drugs</td>
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<td></td>
<td>- Post-launch price cuts</td>
<td>- Adequate protection for patented drug prices</td>
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<td></td>
<td>- Aggressive reference pricing mechanisms</td>
<td></td>
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<tr>
<td>Reimbursement and formulary access</td>
<td>- Narrow, budget-focused decision--making</td>
<td>- Use of science-based health technology assessments</td>
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<td></td>
<td>- Failure to acknowledge cost-effectiveness</td>
<td>- Risk-sharing agreements for costly new drugs</td>
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<td></td>
<td>- Failure to update reimbursement lists on a regular basis</td>
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LARGE PATIENT POPULATIONS ARE GROWING, AND AGING

The BRIC/MIST countries are home to almost half of the entire global population. The group includes four of the world’s five most populous nations; China heads the rankings, with a population numbering almost 1.4 billion, followed closely by India, where numbers are heading rapidly towards the 1.3 billion mark (World Bank, 2016a). Populations in both Indonesia and Brazil are in excess of 200 million, while those in Russia and Mexico comfortably exceed 100 million.

Table 1: Key constraints and drivers of market access in BRIC/MIST markets

<table>
<thead>
<tr>
<th>Area</th>
<th>Constraints</th>
<th>Drivers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Public sector procurement</td>
<td>- Non-transparent purchasing mechanisms</td>
<td>- Open, transparent procurement procedures</td>
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<tr>
<td></td>
<td>- Imposition of compulsory discounts</td>
<td>- Level playing field for local and imported products</td>
</tr>
<tr>
<td></td>
<td>- Preferential treatment for local industry</td>
<td>- Willingness to negotiate reasonably for the purchase of single-source products</td>
</tr>
<tr>
<td></td>
<td>- Failure to impose effective quality requirements</td>
<td></td>
</tr>
<tr>
<td>Prescribing</td>
<td>- Shortage of prescribing expertise</td>
<td>- Specialist training and recruitment initiatives</td>
</tr>
<tr>
<td></td>
<td>- Restrictive prescribing conditions</td>
<td>- Availability of science-based clinical guidelines</td>
</tr>
<tr>
<td>Promotion</td>
<td>- Ambiguous regulations governing promotion</td>
<td>- Clear regulatory guidance on promotional activity</td>
</tr>
<tr>
<td></td>
<td>- Provider restrictions on rep visits</td>
<td>- Effective policing of regulations, delivering a level playing field</td>
</tr>
<tr>
<td></td>
<td>- Unethical activity by competitors and/or providers</td>
<td></td>
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</tbody>
</table>

GMP = good manufacturing practice

Source: Datamonitor Healthcare
Populations in four of the eight countries are growing at annual rates of more than 1%. With India among these four, and with numbers in China rising by around half that amount, India will replace China as the world's most populous nation by 2025. By then, the aggregate size of the BRIC/MIST population will have risen by a further 283 million, reaching almost 3.8 billion.

Russia is a notable exception to the general trend, with the country's population having declined significantly since the collapse of the Soviet Union some 25 years ago. Emigration has been a factor behind the decline, but low fertility rates, the poor health status of many patients, and shortcomings in healthcare provision have also contributed. Numbers have stabilized in recent years, but a further marginal decline is anticipated through to 2025 (World Bank, 2016a). Elsewhere, while India and China will be responsible for the majority of aggregate population growth in the period to 2025, numbers will rise significantly in Indonesia (30 million), Brazil (17 million), and Mexico (also 17 million).

Additionally, more significant than overall population growth is the fact that BRIC/MIST populations are aging, and will continue to do so at startling rates in some countries. South Korea aside, current populations are young in comparison with those in most developed economies, reflecting a combination of high birth rates and relatively limited life expectancy. Improvements in healthcare provision have begun to drive up longevity, however, and the proportion of patients aged 65 or over

### Table 2: BRIC/MIST populations, current growth rates and 2025 forecasts

<table>
<thead>
<tr>
<th>Country</th>
<th>2014 population (millions)</th>
<th>2014 growth rate (%)</th>
<th>2025 population forecast (millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>China</td>
<td>1,364</td>
<td>0.5</td>
<td>1,409</td>
</tr>
<tr>
<td>India</td>
<td>1,295</td>
<td>1.2</td>
<td>1,462</td>
</tr>
<tr>
<td>Indonesia</td>
<td>255</td>
<td>1.3</td>
<td>285</td>
</tr>
<tr>
<td>Brazil</td>
<td>206</td>
<td>0.9</td>
<td>223</td>
</tr>
<tr>
<td>Russia</td>
<td>144</td>
<td>0.2</td>
<td>142</td>
</tr>
<tr>
<td>Mexico</td>
<td>125</td>
<td>1.3</td>
<td>142</td>
</tr>
<tr>
<td>Turkey</td>
<td>76</td>
<td>1.2</td>
<td>83</td>
</tr>
<tr>
<td>South Korea</td>
<td>50</td>
<td>0.4</td>
<td>52</td>
</tr>
</tbody>
</table>

Source: World Bank, 2016a
will increase significantly over the next 10–15 years.

Figure 1: Population aging in the BRIC/MIST markets, by country, 2015–30

Source: World Bank, 2016b

Individuals aged 65 and over currently account for less than 6% of total patient populations in India and Indonesia, and will still account for less than 9% in 2030 (World Bank, 2016b), but more dramatic changes will be witnessed in most other BRIC/MIST countries. In China, the proportion of elderly patients will rise from 9.6% to 17.2% over the next 15 years. In Russia, the figure will increase from 13.4% to 18.8% during that period, while in South Korea, where seniors already account for 13.1% of the patient population, the figure will reach 23.7% by 2030.

Aging patient populations will have major implications for healthcare systems in the BRIC/MIST markets. Shifting dependency ratios will mean a smaller proportion of the population pays taxes used to finance public healthcare provision. At the same time, demand for government-funded care will quicken, reflecting the fact that elderly patients are high-level consumers of healthcare services. Pressure on health system finances will build as a result, driving the pursuit of stronger cost-containment measures.

EPIDEMIOLOGICAL TRENDS ARE SHIFTING

Immunization programs, access to treated water, and improved sanitation have reduced the burden imposed by infectious diseases on populations in many developing countries, including a number of BRIC/MIST markets. At the same time, changing lifestyles and dietary habits have combined with increasing longevity to drive the emergence of chronic NCDs as a growing threat to patient health.
NCDs now account for more than 80% of all deaths in Russia, China, South Korea, and Turkey, and for more than 70% of overall mortality in Brazil, Mexico, and Indonesia. The burden imposed by individual diseases varies widely, often reflecting the prevalence of risk factors such as tobacco and alcohol consumption, and obesity.

Cardiovascular diseases account for 60% of all deaths in Russia, where they are a major contributor to the 11-year gap between male (65 years) and female (76 years) life expectancy at birth (World Bank, 2016b). Almost 60% of the country's adult males are smokers, while alcohol consumption is also high among the male population (WHO, 2016a). Tobacco consumption is a significant contributing factor to the rising incidence of cancer in countries such as Russia, Turkey, and South Korea. Cancer is now the biggest killer in South Korea, where it is responsible for a 30% share of overall mortality, and cancer also accounts for more than 20% of all deaths in Turkey and China.

Pollution poses an additional risk to the health of growing urban populations in China, where chronic respiratory diseases (CRDs) account for 15% of all deaths. CRDs are responsible for 11% of deaths in India, but are a more modest contributor to mortality in other BRIC/MIST markets. Diabetes is less prevalent in most BRIC/MIST markets, but is imposing huge pressure on Mexico's healthcare system, and is a growing problem in Brazil. Again, disease incidence reflects the relative prevalence of risk factors, with almost one-third of Mexico's adult population classified as obese (WHO, 2016a).

A substantial proportion of NCD cases remain undiagnosed until conditions such as cancer,
cardiovascular disease, and diabetes have reached an advanced stage. Patient outcomes are relatively poor as a result, but have begun to improve where national initiatives to combat NCDs have been established (Schmidt et al., 2011). Such initiatives involve screening programs designed to encourage earlier diagnosis of conditions including cancer and cardiovascular disease, enabling earlier intervention and more positive outcomes. Meanwhile, access to subsidized drugs for the treatment of these conditions has also been broadened. These are dominated by the provision of medicines available in generic form, but the reimbursement of some newer drug classes as part of national NCD treatment programs has opened up new opportunities for some patented multinational brands.

ACCESS TO SUBSIDIZED HEALTHCARE PROVISION HAS INCREASED

Private health cover is the preserve of a small minority in most BRIC/MIST markets, while social health insurance programs in most of the eight countries have, until recently, been either non-existent or limited in terms of their reach. Where that is the case, low-income patients with no health insurance have struggled to access even the most basic of healthcare needs. The situation has improved dramatically in several countries since the turn of the century, however, while efforts to broaden access to subsidized provision are either being pursued or are in the pipeline elsewhere.

The most dramatic change has taken place in China, where two urban health insurance schemes and a co-operative rural health program have been rolled out progressively since 2009. By the early part of this decade, around 95% of the population was covered by one of the three initiatives (Blumenthal and Hsiao, 2015).

Elsewhere, existing schemes are being expanded or merged in a drive to achieve universal basic health coverage. That process was already complete in South Korea by 2000, but has since become a reality in both Turkey and Mexico, while Indonesia embarked on the rollout of a national health insurance scheme at the beginning of 2014. Existing social health insurance schemes in Turkey were merged in 2003 as part of the country's health transformation program, while coverage was extended to previously uninsured individuals in 2008. In Mexico, more than 50 million uninsured patients have been enrolled into a "people's health insurance" (Seguro Popular) program that will eventually be merged with existing social security and civil service schemes.

The universal right to healthcare – free at the point of delivery – is enshrined in Brazil’s constitution, while Russia’s compulsory health insurance system provides in theory for universal basic access to subsidized provision. The majority of India’s 1.3 billion population remain uninsured, however, with a succession of governments there having failed to deliver on ambitious pledges to increase coverage.

The range of benefits available to insured patients in most of the eight countries remains limited, and strengthening coverage is high on the health policy agenda. Funds available to bankroll these initiatives are in short supply, however, and near-term progress in several countries will be limited by budget constraints. Coverage plans in Russia and Brazil are most vulnerable to deteriorating economic conditions, which have seen the Brazilian government slash funding for some subsidy programs, and which could force policymakers in Russia to postpone the planned rollout of a universal outpatient reimbursement scheme.
HEALTH EXPENDITURE IS RISING, BUT REMAINS LIMITED

Coupled with rising incomes, reform programs have sharply driven up healthcare spending in several BRIC/MIST countries since the turn of the century. The proportion of GDP devoted to healthcare in South Korea rose from 4.2% to 7.4% between 2000 and 2014 (WHO, 2016b). Over the same period, the sector’s share of GDP also rose by 1% or more in Brazil, Russia, and Mexico, while more modest increases were observed in India, China, Indonesia, and Turkey.

National spending on healthcare is now equivalent to 8.3% of GDP in Brazil, and exceeds 7% of GDP in Russia and South Korea. However, spending in the sector is still equivalent to less than 5% of GDP in India, while in Indonesia the figure stands at just 2.8%. Since GDP in some BRIC/MIST countries is far lower than in the world’s most developed markets, this means per capita spending on healthcare is also limited. At purchasing power parity, per capita spending on healthcare in both India and Indonesia is less than one tenth of the OECD average (WHO, 2016b, OECD, 2015). Notwithstanding recent rapid increases, it remains below $750 in China, while South Korea is the only BRIC/MIST country in which annual per capita health spending exceeds $2,500 (WHO, 2016b).
In most cases, recent increases in national health expenditure have been spearheaded by a period of expansive government investment in public health infrastructures, and by costs associated with the establishment or expansion of social health insurance schemes. In China, the government’s contribution to national health expenditure has risen from around 38% to almost 56% since 2000, while in Turkey the government’s share has increased from less than 63% to more than 77%. Significant though less spectacular increases have also been witnessed in Brazil, Mexico, and South Korea (WHO, 2016b).

However, government budgets have come under growing pressure during the past two to three years, prompting a more conservative approach to public health expenditure. This has seen public sector contributions to total spending on healthcare level off or, as in Russia, decline. There, the government’s share of national health expenditure has fallen from a peak of more than 64% to a current level of just over 52% (WHO, 2016b).

Elsewhere, despite recent increases, government contributions to national healthcare spending remain generally low by international standards. Public funds underpin only 46% of national health expenditure in Brazil, 38% in Indonesia, and a paltry 30% in India. The figure is highest in Turkey, where the government is responsible for more than three-quarters of national health spending, while public funds account for 50–56% of the total in Russia, China, Mexico, and South Korea (WHO,
PATIENTS STILL FOOT A SUBSTANTIAL PROPORTION OF HEALTHCARE AND PHARMACEUTICAL COSTS

While government health funding has increased appreciably in most BRIC/MIST markets, patients are still heavily exposed to healthcare costs. This has major implications in low-income countries, where many patients are unable to pay for their healthcare needs in full.

Healthcare spending in India and Indonesia is still underpinned predominantly by private funds, which account for 70% and 62% of respective health expenditure totals. In turn, private spending is dominated by out-of-pocket (OOP) payments made by patients. These account for 89% of all private spending in India, where patients foot more than 62% of the country’s entire healthcare bill (WHO, 2016b).

OOP payments account for between 44% and 47% of national health expenditure in Indonesia, Russia, and Mexico, and for 36% in South Korea. Patients are least exposed to healthcare spending in Brazil, where OOP payments account for just over a quarter of national health expenditure, and Turkey, where the figure stands at less than 18% (WHO, 2016b).

The proportion of patients with private health cover remains extremely low in most BRIC/MIST markets.
markets; less than 5% of private healthcare spending is backed by health insurance plans in Russia, India, Indonesia, and Turkey (WHO, 2016b). Figures for Mexico, China, and South Korea are little higher, leaving Brazil as the only one of the eight countries in which spending by private payers is a really significant contributor to national health expenditure totals.

Even where private health insurance is relatively prevalent, many plans focus on hospital cover, and few offer outpatient drug benefits. This means patients are exposed to the bulk of costs associated with medicines prescribed outside the hospital setting. As a result, their contribution to drug spending in most BRIC/MIST markets is even higher than their share of total health expenditure.

With generics prescribed wherever possible in the public hospital sector, and with many patients unable to afford original brands, demand for multinational products is distinctly limited in low-income BRIC/MIST markets. More substantial opportunities for originators have emerged where government-funded provision of drugs for the treatment of "catastrophic" diseases has been established. Access to the formularies associated with such initiatives is closely controlled, however, while restrictive budgets often limit patient access to listed products. The most prominent exception to this rule is in Brazil, where thousands of patients have pursued their constitutional right to healthcare through the courts in a bid to access innovative medicines not listed on the country's specialist pharmaceutical assistance program (CEAF; Componente Especializado da Assistência Farmacêutica) formulary.

*The BRIC/MIST pharma markets*

**RISING STARS**

Rising incomes and improved access to subsidized provision have driven a surge in demand for healthcare across the BRIC/MIST markets. These trends have also triggered a sustained increase in drug consumption, and rising volumes have been a significant contributor to recent strong growth in the value of the eight BRIC/MIST pharmaceutical markets.

In 2003, six of the eight BRIC/MIST countries were ranked among the world's 20 biggest pharmaceutical markets (RSC, 2009). Ten years later that figure had risen to seven, while recent forecasts indicate that the eighth – Indonesia – will claim a top 20 ranking before the end of this decade (DCAT, 2015).

Back in 2003, China occupied ninth place in the rankings. By 2008 it had climbed to fifth position, while by 2013 it had become the world's second biggest pharmaceutical market. In the 10-year period between 2003 and 2013, Brazil rose from 10th to sixth place in the rankings; South Korea climbed from 17th to 15th position; while Russia, which was ranked outside the top 20 in 2003, occupied 11th place a decade later (DCAT, 2015).

Forecasts calculated using constant exchange rates anticipate a further climb up the rankings for most BRIC/MIST markets through the second half of this decade (DCAT, 2015). China will consolidate its position as the world's second biggest pharmaceutical market, while Brazil, Russia, India, South Korea, and Turkey are all expected to occupy loftier positions in 2018 than they did five years earlier.
<table>
<thead>
<tr>
<th>Rank</th>
<th>2003</th>
<th>2008</th>
<th>2013</th>
<th>2018</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>US</td>
<td>US</td>
<td>US</td>
<td>US</td>
</tr>
<tr>
<td>2</td>
<td>Japan</td>
<td>Japan</td>
<td>China</td>
<td>China</td>
</tr>
<tr>
<td>3</td>
<td>Germany</td>
<td>France</td>
<td>Japan</td>
<td>Japan</td>
</tr>
<tr>
<td>4</td>
<td>France</td>
<td>Germany</td>
<td>Germany</td>
<td>Germany</td>
</tr>
<tr>
<td>5</td>
<td>Italy</td>
<td>China</td>
<td>France</td>
<td>Brazil</td>
</tr>
<tr>
<td>6</td>
<td>UK</td>
<td>Italy</td>
<td>Brazil</td>
<td>France</td>
</tr>
<tr>
<td>7</td>
<td>Spain</td>
<td>UK</td>
<td>Italy</td>
<td>UK</td>
</tr>
<tr>
<td>8</td>
<td>Canada</td>
<td>Spain</td>
<td>UK</td>
<td>Italy</td>
</tr>
<tr>
<td>9</td>
<td>China</td>
<td>Canada</td>
<td>Spain</td>
<td>Canada</td>
</tr>
<tr>
<td>10</td>
<td>Brazil</td>
<td>Brazil</td>
<td>Canada</td>
<td>Russia</td>
</tr>
<tr>
<td>11</td>
<td>Mexico</td>
<td>Mexico</td>
<td>Russia</td>
<td>India</td>
</tr>
<tr>
<td>12</td>
<td>Australia</td>
<td>Turkey</td>
<td>Mexico</td>
<td>Spain</td>
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<tr>
<td>13</td>
<td>India</td>
<td>India</td>
<td>India</td>
<td>Mexico</td>
</tr>
<tr>
<td>14</td>
<td>Poland</td>
<td>South Korea</td>
<td>Australia</td>
<td>South Korea</td>
</tr>
<tr>
<td>15</td>
<td>Netherlands</td>
<td>Australia</td>
<td>South Korea</td>
<td>Australia</td>
</tr>
<tr>
<td>16</td>
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<td>Greece</td>
<td>Argentina</td>
<td>Turkey</td>
</tr>
<tr>
<td>17</td>
<td>South Korea</td>
<td>Poland</td>
<td>Poland</td>
<td>Saudi Arabia</td>
</tr>
<tr>
<td>18</td>
<td>Turkey</td>
<td>Netherlands</td>
<td>Turkey</td>
<td>Poland</td>
</tr>
<tr>
<td>19</td>
<td>Portugal</td>
<td>Belgium</td>
<td>Belgium</td>
<td>Argentina</td>
</tr>
<tr>
<td>20</td>
<td>Greece</td>
<td>Russia</td>
<td>Netherlands</td>
<td>Indonesia</td>
</tr>
</tbody>
</table>

Source: DCAT, 2015; RSC, 2009
CHINA DOMINATES IN OVERALL VALUE TERMS...

By 2015, pharmaceutical markets in the eight BRIC/MIST countries were worth an aggregate of more than $200bn (BMI Research, 2016a, 2016b, 2016c, 2016d, 2016e, 2016f, 2016g, 2016h). China, with sales of $109bn, was the dominant contributor to that total, accounting for almost 54%. No other BRIC/MIST pharmaceutical market was worth more than $20bn, but annual sales exceeded $15bn in Brazil, Russia, India, and South Korea, while the Mexican market was valued at more than $11bn. Turkey (with 2015 sales of $7.6bn) and Indonesia ($5.8bn) were the group’s two smallest markets.

<table>
<thead>
<tr>
<th>Country</th>
<th>2015 sales ($bn)</th>
<th>Share (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>China</td>
<td>109.0</td>
<td>53.9</td>
</tr>
<tr>
<td>Brazil</td>
<td>20.0</td>
<td>9.9</td>
</tr>
<tr>
<td>Russia</td>
<td>16.6</td>
<td>8.2</td>
</tr>
<tr>
<td>India</td>
<td>17.0</td>
<td>8.4</td>
</tr>
<tr>
<td>South Korea</td>
<td>15.1</td>
<td>7.5</td>
</tr>
<tr>
<td>Mexico</td>
<td>11.2</td>
<td>5.5</td>
</tr>
<tr>
<td>Turkey</td>
<td>7.6</td>
<td>3.7</td>
</tr>
<tr>
<td>Indonesia</td>
<td>5.8</td>
<td>2.9</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>202.3</strong></td>
<td><strong>100.0</strong></td>
</tr>
</tbody>
</table>

Source: BMI Research, 2016a, 2016b, 2016c, 2016d, 2016e, 2016f, 2016g, 2016h
...BUT ORIGINATOR SHARES OF THE BRIC/MIST PIE ARE HIGHER ELSEWHERE

Originators have invested heavily in most BRIC/MIST countries, targeting a slice of markets that are expanding rapidly and that possess huge long-term growth potential. The proportion of patients able to afford original brands is limited in most emerging markets, while governments that fund the provision of subsidized medicines purchase generics wherever possible. This has limited levels of penetration achieved by originators in most BRIC/MIST markets, but experience has shown that their brands can enjoy lengthy and successful lifecycles, even when faced with competition from generic copies. This is a reflection in part of the premium which prescribers and patients place on quality in markets where low-cost, substandard generics and copies have traditionally circulated widely.

Notwithstanding this preference for original brands, the combined impact of modest government drug budgets and low patient incomes imposes an often severe constraint on demand for such products. Since patients in most emerging markets are exposed to a substantial proportion of pharmaceutical costs, there is often a strong correlation between per capita incomes and demand for original brands. Where subsidized access to innovative drugs is available, this can deliver a substantial boost to prospects for originators, however, and ranking BRIC/MIST markets by sales of original brands generates outcomes that bear little relation to overall market values.

As recently as 2012, the market for original brands in Brazil was worth more than its equivalent in

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**Figure 5: Shares of the BRIC/MIST market countries, 2015**

Source: BMI Research, 2016a, 2016b, 2016c, 2016d, 2016e, 2016f, 2016g, 2016h
China, despite the fact that total pharmaceutical sales in China were more than twice as high as those in Brazil. Originator shares of markets in Mexico, Russia, and Turkey are also significantly higher than those in lower-income countries such as China, India, and Indonesia. Aggregate sales achieved by original brands in Brazil, Mexico, Russia, and Turkey during 2012 were more than double those in China (IMS Health, 2013). These figures explain why, while China may dominate BRIC/MIST pharmaceutical sales in overall value terms, other, much smaller markets are of considerable interest to originators.

MARKET GROWTH IS STILL GENERALLY STRONG, BUT CURRENCY FACTORS COMPLICATE THE PICTURE

Pharmaceutical market growth rates in China and several other BRIC/MIST countries have moderated in the face of slower economic growth. Slowdowns are relative, however, and growth rates across the eight countries remain significantly higher than those in most developed pharmaceutical markets. In local currency terms, pharmaceutical sales in China, Russia, India, and Indonesia are expected to rise at double-digit rates during 2016 (BMI Research, 2016d, 2016b, 2016c, 2016f), while growth in Turkey will fall just short of 10% (BMI Research, 2016h). Growth in Brazil is anticipated to be more than 7%, while sales in Mexico and South Korea are forecast to increase by around 3% (BMI Research, 2016a, 2016e, 2016g).

Currency movements exert a constant impact on multinational businesses, but exchange rate volatility has emerged as a more significant threat to originator business in emerging markets since the beginning of 2015. Currencies in several countries have either been devalued by governments or have declined significantly in strength against the US dollar. This has eroded dollar-based sales reported by multinationals in affected markets, and has posed additional problems in countries where drug prices are subject to regulatory control, since this limits the ability of companies to adjust prices in response to changing cost structures.

Most BRIC/MIST currencies are expected to decline further in value against the dollar during 2016. This will erode dollar-based market growth in some of the eight countries, and will wipe it out completely in others, prompting a decline in their overall dollar value. As a result, while local currency sales growth remains strong in most BRIC/MIST countries, aggregate pharmaceutical sales across the eight markets are expected to rise by just 2.3% to $206.9bn during 2016 when expressed in dollars.
Table 6: Impact of currency movements on the value of BRIC/MIST markets, by country, 2015–16

<table>
<thead>
<tr>
<th>Country</th>
<th>2015 sales ($bn)</th>
<th>2016 local currency growth (%)</th>
<th>2016 dollar growth (%)</th>
<th>2016 sales forecast ($bn)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brazil</td>
<td>20.0</td>
<td>7.4</td>
<td>-10.6</td>
<td>17.9</td>
</tr>
<tr>
<td>Russia</td>
<td>16.6</td>
<td>18.9</td>
<td>1.1</td>
<td>16.8</td>
</tr>
<tr>
<td>India</td>
<td>17.0</td>
<td>11.8</td>
<td>5.1</td>
<td>17.5</td>
</tr>
<tr>
<td>China</td>
<td>109.0</td>
<td>11.7</td>
<td>5.6</td>
<td>116.0</td>
</tr>
<tr>
<td>Mexico</td>
<td>11.2</td>
<td>3.0</td>
<td>-7.6</td>
<td>10.3</td>
</tr>
<tr>
<td>Indonesia</td>
<td>5.8</td>
<td>10.2</td>
<td>3.3</td>
<td>6.0</td>
</tr>
<tr>
<td>South Korea</td>
<td>15.1</td>
<td>3.2</td>
<td>-2.7</td>
<td>14.7</td>
</tr>
<tr>
<td>Turkey</td>
<td>7.6</td>
<td>9.7</td>
<td>0.9</td>
<td>7.7</td>
</tr>
</tbody>
</table>

Source: BMI, 2016a, 2016b, 2016c, 2016d, 2016e, 2016f, 2016g, 2016h
Accessing the BRIC/MIST pharma markets

Making significant inroads into the BRIC/MIST markets has proved challenging for multinational pharmaceutical companies. Cultural and logistical issues aside, they have been confronted with deficient or ineffective intellectual property protection laws, and by regulatory frameworks that often differ markedly from those in their traditional core markets, which have been harmonized progressively through initiatives such as the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. In low-income BRIC/MIST countries, companies have also been forced to come to terms with a very different set of market dynamics, where affordability is a key issue for both governments and the vast majority of patients, and where the behavior of prescribers, providers, and patients is often unfamiliar.

BIG PHARMA’S LEVERAGE IS OFTEN LIMITED

A powerful lobbying force in its traditional core markets, the multinational pharmaceutical industry has found that its ability to shape health policy agendas in many BRIC/MIST countries is more limited. This is the result in part of financial factors, which rule out government-funded subsidies for most innovative new drugs. Political factors are also often at play, however, especially where local manufacturers are important suppliers of low-cost drugs.
Governments in countries with substantial domestic pharmaceutical industries have been reluctant to impose regulations that might jeopardize local manufacturers – not only because of the potential implications for low-cost generic availability, but also because of the impact they may have on employment, industrial output, and export revenues. The desire to protect the interests of local manufacturers has also acted as a barrier to the removal of import tariffs, and has driven the retention or establishment of drug pricing and/or procurement mechanisms that favor domestic producers.

While many prescribers and patients express a preference for original brands, the image of the companies that manufacture them remains poor in some BRIC/MIST markets. Big Pharma’s ill-judged management of the controversy surrounding access to patented antiretroviral (ARV) drugs in Africa during the 1990s and early 2000s still casts a shadow.

Described later as “a mistake” by former Novartis chief executive officer Daniel Vasella (Fisher and Rigamonti, 2005), the industry’s approach to the ARV pricing affair was a factor behind the decision to clarify compulsory licensing provisions in the World Trade Organization’s agreement on trade-related aspects of intellectual property rights at Doha in 2001. In turn, the Doha Declaration gave some governments – including those in three BRIC/MIST markets – the conviction to issue compulsory licenses for the local manufacture or import of patented drugs.

Since then, originators have pursued an increasingly flexible approach in developing markets, where patient access programs and agreements with governments on access to costly patented drugs are now commonplace. Big Pharma remains a soft political target, however, and has been scapegoated by some governments keen to paper over cracks in the healthcare systems over which they preside. As a result, originators have been forced to tread carefully in their drive to secure improvements in market access. Where significant progress has been achieved in recent years, it has often owed more to bilateral trade deals or multinational treaty obligations than to direct industry lobbying at a national level.

PRESSURE ON HEALTHCARE FINANCES HAS INTENSIFIED, AND WILL HINDER MARKET ACCESS

The market access climate in BRIC/MIST countries remains complex, variable, and subject to rapid change. It is being driven variously by health system reforms, healthcare funding issues, pressure exerted by non-industry stakeholders, international treaty obligations, and commitments made by governments to major trading partners. These factors exert conflicting pressures on governments, which must weigh the economic, political, and social implications of policy decisions.

Economies in most BRIC/MIST countries have slowed appreciably, while those in Brazil and Russia contracted sharply in 2015. Healthcare finances have come under growing pressure as a result, and the financial connotations of health policy decisions have taken on renewed importance. The deteriorating economic climate in Brazil has already seen policymakers slash budgets for some publicly funded pharmaceutical access programs. In Russia, meanwhile, the recession will almost certainly delay plans for the establishment of a national reimbursement scheme.
Financial pressures may be less intense in other BRIC/MIST countries, but with most governments shouldering a larger proportion of healthcare costs in the wake of recent reforms, cost-containment will be a priority as economic growth slows. Drug spending will be a favored target, and pharmaceutical cost-containment initiatives, including restrictive pricing and reimbursement policies, will act as a barrier to market access for costly new drugs.

Financial considerations will also mitigate against the introduction of stronger intellectual property protection in some BRIC/MIST markets, where policymakers will be keen to avoid the imposition of constraints on access to low-cost generics. This will see some governments drag their feet on pledges to implement more effective patent protection regimes. It could even see some pursue compulsory licensing of more patented drugs.

**BUT CALLS FOR IMPROVED ACCESS TO NEW DRUGS WILL HELP TRIM REGULATORY REVIEW TIMES**

One of the few areas likely to be unaffected by healthcare funding considerations is pharmaceutical registration. Here, BRIC/MIST governments are under growing pressure to improve patient access to innovative new drugs, especially where the products in question address unmet medical needs or offer significant clinical improvements over existing treatments.

Some have already responded to such calls, boosting medicines agency budgets, overhauling review procedures, and introducing or expanding fast track approval pathways. Others have signaled their intent to address approval backlogs and drug lag times. Coupled with the relaxation or reform of clinical trial requirements, this will begin to have a positive impact on new drug approval times in several BRIC/MIST markets.

**NON-FINANCIAL BARRIERS TO THE UPTAKE OF INNOVATIVE DRUGS**

Combined sales of innovative new drugs in the four BRIC markets, Mexico, and Turkey are lower than those in France alone, both one year and five years after launch in those six countries (Shankar, 2015). This is despite the large pool of patients requiring treatment for conditions addressed by most new medicines being brought to market in these countries.

Funding is undoubtedly a major barrier to the uptake of new drugs in these markets. Other factors are also at play, however, and while patient access programs, country-specific pricing, or tiered pricing strategies can boost sales of multinational brands in emerging markets, originators have begun to acknowledge the need to adopt more nuanced strategies in order to broaden uptake of their products.

Awareness, accessibility, affordability, and treatment adherence are among the key non-financial barriers to new drug uptake in emerging markets (Shankar, 2015). By adopting more sophisticated access strategies and working with a broader range of stakeholders, all of these factors can be addressed to some extent.

Partnerships with health authorities and the medical profession can help not only to raise awareness of individual diseases, but also to encourage more widespread screening and diagnosis. By enabling
earlier intervention, this has the potential to improve patient outcomes, and to reduce costs imposed on healthcare systems by the treatment of severe, late-stage cases.

By working with distributors and pharmacists as well as health authorities, problems regarding the availability of drugs can be addressed, ensuring that a larger proportion of diagnosed patients can access prescribed medicines. Pharmacists can also play a key role in improving patient adherence to treatment protocols, which is often poor in emerging markets.

While the successful implementation of these strategies can help to boost commercial prospects for innovative new drugs, some formidable barriers to market access remain. Chief among these in several BRIC/MIST markets are deficiencies in public healthcare provision. Underfunded public health infrastructures often struggle to cope with demand, especially where access to subsidized provision has been increased.

Equally important in several countries is a chronic shortage of qualified health professionals, and staff shortages are often most acute in specialist fields. Given the types of products that now dominate both the portfolios and late-stage pipelines of many originator companies, this is a particularly relevant issue. Put simply, there is little point in developing, registering, and attempting to market an innovative new drug if the expertise required to diagnose and treat the condition it targets does not exist.

Where governments are attempting to train and recruit more specialists in fields such as oncology, they face an uphill struggle. Salaries and working conditions are often significantly better in the private sector, while qualified medical specialists can usually earn more by practicing abroad. With chronic conditions such as cancer and cardiovascular disease now the leading causes of death in most BRIC/MIST countries, the need for more trained oncologists and cardiologists is increasingly urgent.

Bibliography


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INTELLECTUAL PROPERTY PROTECTION

The ability to obtain and uphold intellectual property (IP) protection rights can affect decisions regarding not only the launch of a new drug, but also whether clinical development work and/or manufacturing activity will be conducted locally. Securing and prosecuting IP rights poses challenges in most BRIC/MIST markets (Brazil, Russia, India, China, Mexico, Indonesia, South Korea, and Turkey), either because IP protection frameworks confer limited levels of protection or because existing regulations are not enforced adequately.

Ineffective IP protection may mitigate against the launch of new drugs in countries where experience has shown that original brands will be exposed to competition from generic copies at a very early stage, and that patent holders will struggle to remove infringing copies from the market. A study by US academics, which examined data on 184 drugs approved by US regulators between 2000 and 2009, found that half of those products reached the market in India more than five years after their initial launch. In turn, over half of all products launched in India were exposed to competition from generic copies within one year of their introduction there (Berndt and Cockburn, 2014).

On IP protection criteria, only two BRIC/MIST countries are ranked among the top 50 of 140 markets surveyed in the World Economic Forum’s latest Global Competitiveness Report (World Economic Forum, 2016). Ironically, those two countries are Indonesia and India – both of which have posed major problems for multinational pharmaceutical companies attempting to lay claim to, and prosecute, their IP rights.
International obligations versus local stakeholder interests

Broadly speaking, the IP protection climate has improved gradually in most emerging markets since the turn of the century. This trend has sparked a growing debate on access to medicines, however, while a desire on the part of governments to maximize the availability of low-cost drugs – and to protect the interests of local manufacturers – has affected both the content of national legislation and the propensity of regulators to administer laws effectively.

Patent laws are well established in most BRIC/MIST markets, but several have been the subject of significant recent change. In many cases, this has been driven by a combination of national obligations under international treaties and pressure exerted by developed-country trading partners. Local stakeholders have pushed back against the introduction of tighter IP laws in some countries, however, and not all recent developments have been positive for originators.

All eight BRIC/MIST countries are members of the World Trade Organization (WTO). As such, they are bound by the WTO’s 1995 agreement on trade-related aspects of IP rights (TRIPS). In practice, IP protection frameworks in several BRIC/MIST markets do not comply fully with TRIPS requirements, but the pursuit of stronger IP protection has seen originators involved in a long, often fruitless, struggle. Where significant progress has been made on paper, governments, regulatory agencies, and courts have often failed to fulfil new requirements in practice.

Table 7: Global competitiveness rankings for BRIC/MIST intellectual property protection frameworks

<table>
<thead>
<tr>
<th>Country</th>
<th>Ranking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indonesia</td>
<td>48</td>
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<tr>
<td>India</td>
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<td>China</td>
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<td>Mexico</td>
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<td>Brazil</td>
<td>83</td>
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<tr>
<td>Russia</td>
<td>124</td>
</tr>
</tbody>
</table>

Patent enforcement, linkage, and data protection are key targets for improvement

Key issues for originators include the weak enforcement of existing patent regulations, the absence of effective patent linkage mechanisms, and regulatory data protection failures. Shortcomings in these areas have combined to expose patented brands to unfair generic competition, and have also hindered efforts by originators to remove infringing products from the market or to claim adequate compensation for loss of revenues. Restrictive patentability criteria and the ability of patent offices to deal with patent applications in a timely fashion are other common problems, while the threat posed by compulsory licensing, both actual and potential, remains a subject of concern for originators.

With patent terms calculated from the date of filing, application backlogs and lengthy review periods limit actual patent terms in several BRIC/MIST markets, and South Korea is the only country in which applicants are compensated for such delays. Patent terms may also be extended there, and in Russia, where regulatory delays eat significantly into protection periods, but patent term extension (PTE) provisions have not been implemented elsewhere.
The restrictive nature of patentability criteria is a concern for originators in all four of the BRIC markets. These have received most publicity in India, where the controversial Section 3(d) of the country’s 2005 Patent Law has been used to deny patents on a number of high-profile multinational brands, and where second-use patents are not recognized. In China, demands for the inclusion of detailed trial data in support of patent applications, coupled with the refusal of regulators to accept post-application data submissions, have also seen originators denied patents that have been granted widely elsewhere (PhRMA, 2016).

Bolar-type early working provisions are a feature of most BRIC/MIST IP frameworks, encouraging the prompt arrival of generics on the market following patent expiries. Proposed amendments to China’s Drug Registration Regulations (DRR) would allow generics companies to conduct development work at any point during the patent period. They would also enable regulators to register generics while a patent on the original drug is still in force, ensuring that competing products were able to enter the market immediately upon patent expiry (Sidley, 2013).

The protection of undisclosed data submitted in support of new drug approvals remains a thorny issue for originators in most emerging markets. Where explicit data protection periods are recognized, these may only be available for data supporting new chemical entities. In China, regulations are even more restrictive, with protection offered only to new drugs that have not been registered in any other country worldwide. Elsewhere, protection periods are either limited or, as in Turkey, eroded by referencing the start of exclusivity periods to foreign approvals. Even where reasonable protection is offered on paper, data exclusivity provisions are often undermined by the propensity of regulators to register generics via reference to data packages submitted by originators in other countries.

**Compulsory licensing remains a threat in some countries**

TRIPS rules allow governments to override patents in certain exceptional circumstances by issuing compulsory licenses for the manufacture or import of generic alternatives to patented drugs. These were clarified in the WTO’s 2001 Doha Declaration.

Governments in three of the eight BRIC/MIST markets have circumvented pharmaceutical patent rights in a bid to source low-cost medicines since then. Calls for compulsory licensing have been resisted by other BRIC/MIST governments to date, and trading implications will likely rule out such action in Mexico and South Korea. The threat of compulsory licensing will be used by regulators in some other countries to lever down the prices of costly patented medicines, however, while the authorities in Russia have begun to show a growing interest in the use of the mechanism as a tool with which to source some innovative drugs more cheaply.

Indonesia became the first of the eight BRIC/MIST countries to break a pharmaceutical patent when, in 2004, it issued compulsory licenses for the manufacture of generic lamivudine (Shire’s Epivir) and nevirapine (Boehringer Ingelheim’s Viramune) (PhRMA, 2016). Efavirenz (Merck & Co’s Sustiva) became the third antiretroviral (ARV) drug subject to a compulsory license in Indonesia during 2007, while a presidential decree in September 2012 issued “government use” licenses for the generic supply of seven patented HIV and hepatitis B treatments (IHS Markit, 2012).
The 2012 decree renewed the compulsory license for efavirenz and allowed for the supply of six other patented ARVs for government use in generic form. It granted royalties equivalent to 0.5% of net sales to patent holders. Under the terms of the decree, compulsory licenses on all seven products were to remain in force until the expiry of originator patents (IHS Markit, 2012).

The Brazilian government began using the threat of compulsory licensing to secure heavy discounts on patented ARVs in the wake of the 2001 Doha Declaration. Substantial discounts were secured on a number of patented ARVs, but, having failed to negotiate what it deemed to be an acceptable price for Merck & Co’s Stocrin (efavirenz), the government issued a compulsory license for the import and local manufacture of generic efavirenz in 2007 (ICTSD, 2007). It began purchasing generic efavirenz for the first time in 2009. The term of the compulsory license was extended after Merck secured patent protection on a crystalline form of the drug, but no other compulsory licenses have been issued (OMPI, 2012).

India became the third BRIC/MIST country to issue a compulsory license in respect of a patented pharmaceutical product in 2012, when it granted Natco Pharma a license to manufacture and sell a generic version of Bayer’s kidney cancer drug, Nexavar (sorafenib). It did so by invoking provisions contained in the country’s 2005 Patent Act, which allow for compulsory licensing where a patent holder fails to make a drug available at “reasonably affordable prices” (ICTSD, 2012).

### Table 8: Compulsory licenses issued by Indonesia in 2012

<table>
<thead>
<tr>
<th>Active substance</th>
<th>Patent holder</th>
<th>Duration of license*</th>
</tr>
</thead>
<tbody>
<tr>
<td>efavirenz</td>
<td>Merck &amp; Co</td>
<td>Until 7 August 2013</td>
</tr>
<tr>
<td>abacavir</td>
<td>GlaxoSmithKline</td>
<td>Until 14 May 2018</td>
</tr>
<tr>
<td>didanosine</td>
<td>Bristol-Myers Squibb</td>
<td>Until 6 August 2018</td>
</tr>
<tr>
<td>lopinavir + ritonavir</td>
<td>AbbVie</td>
<td>Until 23 August 2018</td>
</tr>
<tr>
<td>tenofovir</td>
<td>Gilead</td>
<td>Until 23 July 2018</td>
</tr>
<tr>
<td>tenofovir + emtricitabine</td>
<td>Gilead</td>
<td>Until 3 November 2024</td>
</tr>
<tr>
<td>tenofovir + emtricitabine + efavirenz</td>
<td>Gilead</td>
<td>Until 3 November 2024</td>
</tr>
</tbody>
</table>

*In all cases, the end of the duration of the license coincides with the patent expiry date.

Source: Decree of the President Republic of Indonesia, 2012
Key national developments

BRAZIL: DUAL EXAMINATION, PATENT CHALLENGES, AND BACKLOGS FRUSTRATE ORIGINATORS

Brazil’s national patent office (INPI; Instituto Nacional da Propriedade Industrial) has failed comprehensively to deal with a growing backlog of patent applications – to the extent that, by the beginning of 2014, the average time from filing a pharmaceutical patent to it being granted exceeded 10 years (PhRMA, 2016).

Delays have been exacerbated since 1999 by the involvement of the National Health Surveillance Agency (ANVISA; Agência Nacional de Vigilância Sanitária) in the pharmaceutical patent review process, creating what is in effect a dual examination regime (PhRMA, 2016). With ANVISA also tending to apply more restrictive patentability criteria than INPI, this has also heightened levels of uncertainty regarding the likely outcome of patent reviews.

The Federal Attorney General recommended in 2009 that ANVISA should limit its involvement to applications deemed to raise health and safety concerns, but an inter-ministerial group set up to consider the agency’s role granted it much broader powers. As a result, ANVISA continues to review applications before INPI begins its reviews, with the result that applications rejected by ANVISA may not even be examined by the patent office. In 2013, ANVISA enacted a new resolution establishing that patent applications considered to be "strategic and of interest to the Brazilian government" will be subject to a substantive review of patentability requirements by the agency (PhRMA, 2016).

Originators have seen their IP protection rights eroded further since 2013, when INPI issued a binding opinion that seeks to revoke so-called "mailbox patents" issued to drugs for which patent applications were filed between January 1995 and the entry into force of Brazil’s 1996 Patent Law. Article 40 of the law provided for 20-year patents from the date of filing, but allowed for a minimum 10-year protection period from the date of grant. Around 220 applications were granted a minimum of 10 years of patent protection under this provision, having not been reviewed within 10 years of filing (PhRMA, 2016).

Legislation passed more than a decade ago grants explicit data protection periods for veterinary medicines and crop protection products, but pharmaceuticals still do not have access to data exclusivity provisions. In their absence, regulators have registered generics that rely on data submitted by originators to prove the safety and efficacy of their products.

Funds to support the employment of more patent reviewers have been made available to INPI over the past two years, but the office does not appear to have made any significant inroads into its massive backlog. Originators still face sometimes decade-long waits for receipt of patent approvals, while the outcome of patent reviews remains unpredictable – especially given the involvement of ANVISA in the review process. Meanwhile, research-based manufacturers have mounted a legal challenge to the resolution under which the agency conducts substantive reviews of applications deemed to be of strategic interest to the government (PhRMA, 2016).

Separately, INPI will continue to pursue the revocation of mailbox patents by filing lawsuits in Federal
District Courts. By 2015, the office had filed suits against the holders of 48 mailbox patents; 18 of the cases had been decided, with eight rulings issued in favor of the patent holder but 10 in favor of INPI (PhRMA, 2016).

RUSSIA: PATENT REVOCATIONS AND COMPULSORY LICENSING EMERGE AS POTENTIAL THREATS

There are signs that the IP protection climate in Russia could deteriorate in the near future. The Federal Antimonopoly Service (FAS) has begun to examine the potential imposition of more restrictive patentability criteria, looking in particular at incremental innovations such as new indications, combinations, pharmaceutical forms, and manufacturing methods (PhRMA, 2016). Amendments to the Russian Civil Code drafted by the FAS could also enable regulators to issue compulsory licenses where they deem that a company has abused a dominant market position and refused to supply the local market without reasonable grounds (Kulikova, 2016). These developments could pose additional problems for originators, which have already been frustrated by the failure of regulators and the judiciary to implement existing IP protection rules effectively.

On paper, Russia’s IP protection framework appears advantageous for originators. The Federal Service for Intellectual Property (Rospatent) issues 20-year pharmaceutical product patents, permits patents for second medical uses, and will consider, upon request, applications for patent term extensions of up to five years where applicants have encountered lengthy regulatory delays. There is no patent linkage mechanism, but nor has Russia enacted an explicit Bolar-type early working clause, while as part of its push for WTO membership (secured in 2012), the country’s 2010 Law on the Circulation of Medicines outlined a commitment to provide at least six years of data exclusivity for information submitted in support of marketing approvals (PharmRussia, 2015). Finally, a new IP court was established in 2013 to deal exclusively with IP protection disputes (The Patent Lawyer, 2014).

In practice, however, the situation is less favorable for originators, while there are already signs that Russia may not fulfil some of the key commitments it made in the run-up to WTO accession. The absence of patent linkage has caused particular problems, largely because no mechanism exists via which patent holders can resolve disputes prior to the launch of a generic product they believe infringes their IP rights (PhRMA, 2016). Furthermore, a reluctance on the part of the courts to issue injunctions in pharmaceutical patent infringement cases has enabled generics manufacturers to continue marketing their products while legal proceedings are in progress.

Nor does Russia appear keen to implement the data protection regime outlined in the Law on the Circulation of Medicines. Court rulings in 2015 failed to uphold data protection claims, while provisions contained in the 2010 law have been watered down by subsequent amendments due for implementation in 2016. These allow for the submission of generic registration applications four years after the approval of an original small molecule drug and three years after marketing authorization of a reference biologic medicine (PhRMA, 2016).

Preventing the launch of generics that infringe their IP rights will remain difficult for patent holders, while the lengthy nature of legal proceedings will add to the financial damage caused by such products. Data exclusivity provisions will also fall short of original commitments, encouraging the
early arrival of generic competitors on the Russian market.

**INDIA: NEW GOVERNMENT UNLIKELY TO DELIVER ON BOLD IP PROTECTION COMMITMENTS**

A change of government in 2014 sparked hopes among originators that India's dire IP protection climate may begin to improve. The country's new prime minister, Narendra Modi, pledged to create a "world class" IP environment in India, and has set up a think tank charged with developing a new National Intellectual Property Rights Policy (PhRMA, 2016). But the policy draft approved by the cabinet in May 2016 cedes no major ground on key issues that have been the subject of protracted multinational lobbying since the passage of India's amended patent law in 2005 (Lexology, 2016).

While the 2005 Patent Act triggered the reintroduction of pharmaceutical product patents for the first time in 30 years, it also imposed significant restrictions on the ability of originators to obtain and prosecute IP rights. Opposition to the introduction of stronger IP protection remains widespread, and while Mr Modi assured US President Barack Obama in 2014 that his government would implement recommendations tabled by a bilateral IP working group, progress to date has been distinctly limited (PhRMA, 2016).

The 2005 law does not allow for the grant of second-use patents. Section 3(d) of the 2005 act also precludes the issue of patents for derivatives of known substances unless they offer significant advances in terms of efficacy (PhRMA, 2016). These provisions have been used to refuse patents for a number of innovative drugs, while patents initially granted to some other products have since been revoked. Most of these decisions have been the subject of protracted legal wrangling.

Gilead's hepatitis C drug Sovaldi (sofosbuvir) is among the latest high-profile products to become embroiled in a dispute over their patent status in India. Sovaldi was denied a patent by the Indian Patent Office in 2015, but the Delhi High Court called on the office to conduct a second review of Gilead’s application. In May 2016, the office reversed its original decision, granting a patent for Sovaldi. This triggered an immediate challenge from non-governmental organizations and patient groups that will now see the Delhi High Court review the case once again (Raghavan, 2016).

In the absence of a patent linkage mechanism, generics that originators claim infringe established patent rights are still being granted marketing authorization, often by state-level regulators. Complex judicial procedures mean defending IP rights is both lengthy and expensive, and some originators have reached out-of-court settlements with generics manufacturers rather than pursuing infringement proceedings (PhRMA, 2016).

Where legal judgments favor originators, satisfactory compensation is often lacking. In October 2015, for example, the Delhi High Court upheld Merck & Co’s patents on its Januvia (sitagliptin) and Janumet (sitagliptin + metformin) diabetes drugs, ordering Glenmark to cease the distribution, marketing, and export of copies it had launched in 2013. The court permitted Glenmark to sell remaining stocks of its products, however, and while it ordered Glenmark to pay Merck's legal costs, the judgment did not award Merck compensation for revenues lost since Glenmark had launched its patent-infringing copies (Livemint, 2015).
The establishment of explicit data protection rules has been discussed by policymakers for years, but proposals for the establishment of five-year exclusivity periods have not been acted upon. In the meantime, regulators continue to limit or waive requirements for the submission of clinical data in support of generic registrations, relying on approvals granted in other countries where applicants must submit confidential test data in order to secure marketing authorizations.

Compulsory licensing provisions contained in the 2005 Patent Act were invoked by the government in 2012, when it granted Natco Pharma a license to manufacture and sell a generic version of Bayer’s sorafenib-based kidney cancer drug, Nexavar (ICTSD, 2012). The national Ministry of Health and Family Welfare has requested the compulsory licensing of several other drugs, but no other patents have been overridden to date (Medical Dialogues, 2015). Originators may console themselves with the thought that, while the current government is unlikely to deliver on its commitments, it will at least prevent an even greater deterioration in the IP protection climate.

CHINA: PATENT FILING REQUIREMENTS RELAXED

Restrictive patentability criteria, weak IP enforcement, and the limited nature of data protection provisions pose significant problems for originators operating in China. Regulators have pledged to address some of these issues in bilateral discussions with US trade representatives, but have been slow to deliver on their commitments.

Patent examination guidelines adhered to by the State Intellectual Property Office (SIPO) emerged as a particular cause for concern following their amendment in 2006. The changes triggered a significant increase in levels of experimental data required to support patent filings, and ruled out post-filing submission of additional data. Originators said the requirements were impractical, and that their implementation – which extended to applications filed and granted before 2006 – had resulted in the denial of patents granted in other countries (PhRMA, 2016).

In December 2013, China said current SIPO examination guidelines would be amended to allow for the submission of additional data after initial filings. No official change to the guidelines has been communicated, but analysis shows that, since the beginning of 2014, more than 90% of rejections issued for pharmaceutical compound patents on the basis of insufficient data have subsequently been overturned (MIP, 2015).

Linkage provisions were added to China’s patent law in 2002, but have failed to prevent the registration of generics that infringe the rights of patent holders. The linkage mechanism has been undermined further by the fact that originators have often been unable to resolve resulting disputes prior to the launch of such products. Recent changes to China’s DRR appear unlikely to resolve existing problems (PhRMA, 2016).

Nor have regulatory data protection provisions provided significant protection for originators in practice. Existing rules provide six-year protection periods for data generated in support of new chemical ingredients; however, protection has been afforded only to products that are “new” in a global sense rather than new to the Chinese market, rendering them all but irrelevant. Data protection
provisions are also undermined by the propensity of regulators to approve generics on the basis of originator submissions to foreign agencies (PhRMA, 2016).

Early working provisions for generics developers will be relaxed considerably if proposed amendments to China’s DRR are implemented. Under current rules, generics manufacturers may file for approval up to two years before the expiry of a patent on the reference drug, while approvals may only be granted following patent expiry. Proposed changes would permit the submission of generic applications at any time, and would enable regulators to issue generic registrations while patents are still in force, ensuring the immediate availability of generic alternatives following patent expiry (Sidley, 2013).

MEXICO: LINKAGE MECHANISM STILL INEFFECTIVE

In line with its commitments under the North American Free Trade Agreement, Mexico established a patent linkage mechanism in 2003. It was strengthened in 2012 when the Mexican Institute of Industrial Property began publishing formulation patents. The Federal Commission for the Protection against Sanitary Risk (COFEPRIS; Comisión Federal para la Protección contra Riesgos Sanitarios) does not appear to have implemented linkage provisions consistently, however, and has continued to register some patent-infringing generics (PhRMA, 2016). Weak patent enforcement mechanisms mean originators often struggle to remove such products from the market.

COFEPRIS issued guidelines on regulatory data protection in 2012. These offer exclusivity periods of up to five years, but apply only to data submitted in support of new chemical entities (NCEs). As guidelines, they are also open to potential challenges from generics manufacturers, and originators continue to lobby for the introduction of regulations providing more explicit protection for original data (PhRMA, 2016).

Mexico’s Bolar exemption permits the import of active pharmaceutical ingredients and raw materials contained in a patented drug during the final three years of its patent term for experimental use by manufacturers developing generic versions of the compound in question. There is no limit on raw material import volumes, however, and originators believe some manufacturers may be abusing early working clauses by stockpiling patented drugs (PhRMA, 2016).

INDONESIA: THREAT OF COMPULSORY LICENSING CONTINUES TO LOOM

Compulsory licensing will be the main preoccupation for originators operating in Indonesia, where “government use” exemptions on the manufacture or import of seven patented drugs were issued in 2012 (see “Compulsory licensing remains a threat in some countries,” above). Compulsory licenses issued to date have all concerned ARV drugs, but the possibility that other high-cost products may be targeted in the future cannot be ruled out, given the government’s current drive to broaden access to subsidized medicines.

SOUTH KOREA: TRADE AGREEMENTS DRIVE MAJOR IP PROTECTION OVERHAUL

South Korea has implemented a raft of new IP protection regulations in line with pledges made during trade negotiations with the US and EU. These have seen the introduction of new rules governing
patent term adjustments or extensions, the establishment of explicit data protection terms, and the creation of a patent linkage mechanism. Significantly beneficial for originators on paper, most changes will have a more modest impact in practice.

PTEs of up to five years may already be claimed by applicants to compensate for regulatory delays in South Korea. Changes to the existing system implemented in 2013 restrict eligibility for PTE to NCEs, however, ruling out extended protection periods for combination products, second uses, and incremental modifications (PhRMA, 2016). Since March 2012, applicants have also been able to seek compensation for delays in the patent approval process where these are caused by the Korean Intellectual Property Office (KIPO). Known as patent term adjustments (PTAs), these must be claimed not more than three months after a patent has been issued. Applicants may be eligible for PTAs where the grant of a patent was delayed for more than four years from filing or three years from a request for examination. Where awarded, compensatory terms are equivalent in length to KIPO delays (BRIC Wall, 2014).

The establishment of an explicit patent linkage mechanism was outlined in 2012 amendments to the Pharmaceutical Affairs Law, which were enforced fully in March 2015 (Kasan Insight, 2015). This has seen the creation of a regime loosely resembling established systems in the US, in that:

- The Ministry of Food and Drug Safety maintains a "Green List" of patented pharmaceutical products.

- Generics manufacturers must notify patent holders of applications for the approval of a generic, declaring whether they intend to launch their product following patent expiry or challenge an originator patent.

Early filings and patent challenges are encouraged by the promise of nine-month exclusivity periods and access to fast track reimbursement reviews, and this will discourage the filing of weak or frivolous patent claims. Where an originator believes the approval of a generic would infringe its patent, it may request a stay of up to nine months in the authorization of the product concerned (Kasan Insight, 2015).

Recent changes have also seen the establishment of explicit data exclusivity periods. These provide five years of exclusivity for data submitted in support of NCEs, and three-year exclusivity periods for data filed in support of other new products. While originators have welcomed the establishment of explicit data protection provisions, the new rules will have little impact in practice. Existing pharmacovigilance provisions confer de facto exclusivity periods on NCEs and other new drugs, which must undergo safety monitoring programs lasting six years and four years, respectively. No generic version of an original product may be approved until safety monitoring programs are complete (PhRMA, 2016).

TURKEY: EPC MEMBERSHIP HAS FAILED TO FIX PROBLEMS FOR ORIGINATORS

Turkey has been a member of the European Patent Convention (EPC) since 2000. As such, all patents granted by the European Patent Office (EPO) are validated by the Turkish Patent Institute (TPI).
Nevertheless, weak patent enforcement mechanisms and a failure to provide effective regulatory data protection have continued to pose problems for originators operating in Turkey.

The status of second-use patents emerged as an additional issue of concern in 2014, following a ruling by the Istanbul IP Court that declared second-use medical claims granted by the EPO null and void. The ruling was overturned by the Turkish Supreme Court in 2015, however, confirming the legitimacy of second-use patents (Erciyas and Karakulak, 2015).

A new law designed to address outstanding IP issues was drafted in 2013, but was ditched in the face of widespread criticism. A revised draft released by the TPI in February 2016 contains provisions designed to bring several aspects of national law into line with the EPC, including the introduction of a reformed post-grant opposition system. It fails to provide clarification on some key issues, however, including patentability conditions for biotechnology inventions and second or subsequent medical uses of a known substance or composition (PhRMA, 2016).

Turkey's membership of the EPA has not prevented IP courts reaching decisions that are out of line with those of the EPO, especially where second-use patents are concerned. The absence of explicit rules governing the patentability of biologics means disputes surrounding these products could also be open to interpretation by local courts (Mondaq, 2015).

Originators will continue to press for the introduction of stronger data exclusivity provisions; Turkey's existing regulatory data protection rules provide six years of exclusivity for products registered in the EU. Protection terms begin on the date of marketing authorization in any European Customs Union country, however, and effective protection terms are often eroded significantly by local regulatory and reimbursement delays. With registration and reimbursement procedures often taking around three years to complete, data submitted in support of new drugs may only be protected for two to three years following the receipt of full market access (PhRMA, 2016).

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Emerging markets represent potentially attractive targets for conducting clinical studies on new drugs. Large, often treatment-naïve patient populations and relatively low clinical research costs are among the key advantages they offer. Many also pose significant challenges, however, including a relative dearth of high-quality research centers with the expertise and experience required to conduct trials in accordance with strict multi-country protocols.

Regulatory frameworks governing clinical research have also emerged as a significant barrier to trial activity among some of the BRIC/MIST markets (Brazil, Russia, India, China, Mexico, Indonesia, South Korea, and Turkey). The sector was often poorly regulated when initial surges in trial numbers were witnessed, and an understandable backlash against unethical activity triggered the imposition of highly restrictive regulations in some markets. In others, regulatory frameworks can be inefficient, overly bureaucratic, or poorly administered.

Lengthy trial approval procedures have also proved a particular problem for originators. These can often limit or rule out the participation of local centers in multi-country trials. Where regulators require the inclusion of local trial data in registration dossiers, this means companies must pursue separate local studies, increasing development costs and delaying the submission of requests for registration.

Regulatory requirements aside, local trials can help to lay the foundations for the successful launch of new drugs by familiarizing prescribers and patients with innovative medicines. As a result, even where the absence of local data would not preclude registration, companies may opt to conduct small-scale local trials. Where they do so, they invariably seek the involvement of key opinion leaders within the medical profession, since their influence on other prescribers encourages post-registration uptake of a new drug, and can also help to sway reimbursement or formulary listing decisions.

Clinical trial activity in the BRIC/MIST markets

Although total trial numbers are significantly higher, industry-funded Phase II and Phase III studies provide a more accurate picture of activity likely to result in the development and registration of new drugs.

An analysis of data from the US National Institutes of Health registry, ClinicalTrials.gov, shows that 38% of new industry-funded Phase II/Phase III trials listed on the registry in 2011 related to studies being undertaken in the eight BRIC/MIST markets. By 2015, that figure had fallen to 30%. While the total number of such studies added to the registry globally in 2015 was 6.4% lower than in 2011, the number of new trials being conducted in BRIC/MIST markets was down on 2011 levels by more than 26% (National Institutes of Health, 2016).

While other factors have undoubtedly contributed to the downward trend, regulatory issues have played a significant role in some countries. The most glaring example is India, where inadequate intellectual property protection has severely limited exclusivity periods enjoyed by original brands.
launched since the turn of the century, and where the imposition of new regulations has exposed trial sponsors to substantial additional risks (see below).

More than 100 new industry-funded Phase II/Phase III studies in India were added to the ClinicalTrials.gov registry in 2011, but numbers have dwindled progressively since then, and totaled just 21 in 2015. Sharp declines have also been witnessed in Brazil, Russia, and Mexico – although the recent fall in activity in Mexico may be a result in part of moves towards more widespread acceptance of approvals granted in the US and Europe.

Industry-funded development activity has held up better in China and South Korea. In China, where inefficient trial approval procedures contribute to lengthy market access delays, the scale of commercial opportunities means manufacturers have been willing to confront these challenges. By contrast, South Korea’s continued popularity as a favored location for clinical trials reflects the attraction of a highly efficient trial approval process and the availability of a substantial, high-quality network of specialist trial centers.

China’s share of industry-funded Phase II/Phase III trials added to the ClinicalTrials.gov registry in the eight BRIC/MIST markets rose from less than 12% in 2011 to almost 17% in 2015. During the same period, South Korea’s share increased from just over 20% to almost 29%. The biggest loser has been India, which accounted for less than 3% of new BRIC/MIST trials listed in 2015, compared with a figure of almost 10% in 2011 (National Institutes of Health, 2016).
Key national developments

BRAZIL: CONEP REMAINS A BARRIER TO SHORTER CTA APPROVAL TIMES

Lengthy clinical trial application (CTA) approval procedures have frustrated originators in Brazil, prompting the cancellation of numerous planned studies before approval has even been obtained (Kesselring et al., 2014). Regulators have taken steps to address some of the major bottlenecks in the trial approval process, but there is no evidence to date that these have reversed the recent decline in industry activity (see figure above). Nor, without further change, are existing delays likely to be eliminated.

As well as local ethics committees, trial protocols must be approved by both the National Health Surveillance Agency (ANVISA; Agência Nacional de Vigilância Sanitária) and the National Commission on Ethics in Research (CONEP; Comissão Nacional de Ética em Pesquisa). These two national bodies have been responsible for the bulk of delays, which have seen CTA approval periods average more than 12 months, compared with a theoretical 90-day approval timeline. An analysis of 28 industry-sponsored Phase II and Phase III trials conducted in Brazil between 2007 and 2013 found that the average time taken for approval was 378 days. Approval by local ethics committees was granted on average within 46 days, but approval by CONEP and ANVISA averaged 175 days and 168 days, respectively (Kesselring et al., 2014).

ANVISA has taken a number of steps to cut trial approval times since the beginning of this decade. In 2012, it introduced new electronic submission procedures and rules designed to expedite the process for trial applications already approved in Europe, the US, Japan, Canada, or Australia. In March 2015, the agency published two new regulations (RDC 09/2015 and RDC 10/2015) aligning technical documentation and good clinical practice (GCP) requirements with international norms (Moeller IP Advisors, 2015).

The 2015 regulations also established fixed deadlines for ANVISA CTA reviews. For Phase III clinical trials with synthetic drugs that have been approved in other countries, ANVISA must now complete its review of trial applications within 90 days. Where it fails to do so, applicants may proceed with trials so long as they have received approval to do so from the relevant ethics committees. For Phase I and Phase II clinical trials with biological drugs, or studies being conducted exclusively in Brazil, ANVISA must complete its technical review within 180 days, although where it fails to meet that deadline, applicants must wait for the outcome of the agency’s review before they may proceed with a trial (Moeller IP Advisors, 2015).

CONEP will continue to pose a barrier to more timely CTA approvals unless it, like ANVISA, pursues changes to the way it handles applications. Direct communication between applicants and the committee is not permitted, which means issues must be transmitted through local ethics committees, exacerbating delays. CONEP reviews are also restarted automatically where any pending or outstanding issues have been raised at its previous monthly meeting (Motti, 2015).

RUSSIA: TRADE MINISTRY REJECTS CALL FOR MORE WIDESPREAD LOCAL TRIAL EXEMPTIONS
Hopes that the Russian government may grant more widespread local trial waivers for foreign drugs were dashed in February 2016, when the Ministry of Industry and Trade rejected proposals that would have allowed for the recognition of clinical trial data accepted by regulators in the US and Europe. The proposals had been tabled by the Federal Antimonopoly Service in a bid to broaden the range of new drugs available to Russian patients, which has been affected since the beginning of this decade by provisions contained in the 2010 Law on the Circulation of Medicines (Pink Sheet, 2016).

The 2010 law required the inclusion of local trials in multi-country clinical studies supporting the registration of all new drugs. It also called for the re-registration of existing products that had been on the market for less than 20 years, with new clinical data required in support of many original products subject to that review process (Katsnelson, 2012).

Coupled with the lengthy nature of trial approval procedures, the 2010 law has delayed the arrival of many new drugs on the Russian market (Katsnelson, 2012). Moreover, it has also prompted manufacturers to shelve local launch plans for some drugs – especially where high prices and the absence of government subsidies mean potential volume sales are limited (Katsnelson, 2012).

Regulators have taken some steps to mitigate the impact of the 2010 law, including the establishment of an abbreviated clinical trial approval procedure, which is designed to be complete inside 60 days. Orphan drugs have also been exempted from local trial requirements, and originators had been hopeful that more widespread trial waivers might have been granted (Terralex, 2015). In the end, however, it appears that a desire to reduce levels of reliance on imported drugs – which have been rendered more expensive following the sharp fall in the value of the ruble – outweighed new drug availability considerations in the minds of some powerful factions within the government.

INDIA: TRIAL ACTIVITY DWINDLES IN THE FACE OF TOUGH LIABILITY AND COMPENSATION RULES

In line with its desire to promote investment in pharmaceutical research, the current Indian government has pledged to address some of the issues that have driven a sharp fall in industry-sponsored clinical trial activity. Watering down tough new rules imposed by its predecessor will be a politically sensitive exercise, however, and will risk incurring the wrath of patient organizations.

Regulatory intervention in the sector was triggered by widespread publicity surrounding unexplained patient deaths in clinical trials. This intervention involved the imposition of new regulations governing sponsor liability and patient compensation during the early part of 2013. Notwithstanding the subsequent amendment of some measures, manufacturers say the regulations lack clarity and impose unacceptable risks on trial sponsors. They have warned that few companies are likely to initiate trials in India until outstanding issues have been resolved (PhRMA, 2016). Key points of concern for manufacturers include ambiguities in the definition of trial-related injury, the absence of an appeals mechanism in decisions surrounding causation, and criminal penalties for trial sponsors that deviate from clinical protocols.

Under current rules, new drugs not previously used in India must undergo local trials in order to obtain marketing approval from the Drug Controller General of India. Exemptions from local trial
requirements may only be granted where this is deemed to be in the public interest. A new order issued by the Central Drugs Standard Control Organization in July 2014 provides for the possible waiver of local trial requirements for orphan drugs and new products with indications for the treatment of conditions for which no alternative therapy exists, but the criteria on which such decisions are based are deemed by manufacturers to be both narrow and ambiguous (PhRMA, 2016).

**CHINA: TRIAL APPROVAL AND WAIVER SYSTEMS BEING OVERHAULED IN A BID TO CUT DRUG LAG TIMES**

Rules governing the approval and conducting of clinical trials in China are being overhauled as part of a broader drive to address the country’s substantial drug lag times. Among other things, attempts will be made to address problems that emerged in 2014 following a change of approach by regulators. Implemented towards the end of 2013, the shift rendered local trial waivers more difficult to obtain, and saw applicants that did obtain waivers being asked to resubmit their New Drug Applications – effectively sending them to the back of an increasingly lengthy queue (CIRS, 2015).

These developments compounded existing delays faced by innovators attempting to launch new drugs in China, which are the result in part of lengthy, bureaucratic trial approval procedures. Obtaining approval for clinical studies typically takes at least a year – partly because the China Food and Drug Administration (CFDA) is chronically under-resourced. The agency is recruiting more staff, however, and aims to make more use of external expertise in the future. The relaxation of local trial requirements and expedited trial approval procedures for some new drugs should also help to reduce delays faced by applicants (PhRMA, 2016).

Draft guidelines issued by the CFDA towards the end of 2014 confirmed that data generated at local centers participating in multi-regional clinical trials may be filed in support of requests for the registration of a new drug. This means applicants seeking the approval of such products do not need to conduct separate, China-specific trials. The changes were confirmed by the State Council in 2015 (IHS, 2015).

Since then, the CFDA has outlined further changes that will be pursued in a bid to expedite new drug development and approval procedures. These will involve the simplification of clinical trial approval procedures, while applications for the approval of trials on drugs that offer clinical advantages in the treatment of several key diseases – including cancer, HIV, and tuberculosis – will be reviewed on a priority basis (ChinaBio Today, 2015).

**MEXICO: REGULATORS LOOK TO SPEED UP CTA APPROVAL PROCESS**

As part of a broader drive to improve levels of regulatory efficiency initiated at the beginning of this decade, Mexico’s Federal Commission for the Protection against Sanitary Risk (COFEPRIS; Comisión Federal para la Protección contra Riesgos Sanitarios) introduced new measures designed to cut clinical trial approval times in 2014.

Trial protocols still require approval from both local ethics committees and the agency itself, but applications may now be evaluated by national health institutes and some specialist hospitals. These
bodies have been granted the power to pre-authorize trial protocols, with COFEPRIS rubber-stamping the decisions at a later stage (BMI Research, 2014). In addition, while details of changes must be submitted to regulators, applicants no longer need to wait for official approval of basic amendments to trial protocols before they may proceed with studies. The aim of the changes is to cut COFEPRIS protocol approval times from around 90 days to just 30 days.

**INDONESIA: RESOURCE SHORTAGES AND REGULATIONS LIMIT INDUSTRY TRIAL ACTIVITY**

Only three new industry-funded Phase II or Phase III trials being conducted in Indonesia were added to the ClinicalTrials.gov registry during 2015 – a figure that was the lowest recorded for over a decade (National Institutes of Health, 2016).

A regulatory framework governing the conducting of clinical trials has been in place since the turn of the century. Local trial data are not required to obtain marketing authorization for new drugs, but regulatory barriers, liability issues, and a shortage of qualified trial investigators have all acted as major constraints on the conducting of industry-sponsored trials (Sahoo and Wibowo, 2015).

Among a population of around 250 million, there are only 200 GCP-certified clinical researchers. Insurance cover for global clinical trials is also hard to obtain, while restrictive regulations governing the shipment of biological samples have limited the involvement of Indonesian centers in multi-country trials on innovative biologics. Government support for the training of site staff and investigators has been stepped up, while private institutions also offer training (Sahoo and Wibowo, 2015). Other barriers to clinical research will have to be addressed before a significant increase in multinational-sponsored trial numbers is witnessed, however.

**SOUTH KOREA: POSITIVE CLIMATE CONTINUES TO ATTRACT INDUSTRY INVESTMENT**

South Korea is one of the few BRIC/MIST markets in which industry-sponsored clinical trial activity has held up over the past five years, thanks to a combination of an efficient regulatory framework and the pursuit of government policies designed to attract further investment. Almost 29% of all industry-funded Phase II and Phase III trials added to the ClinicalTrials.gov registry in BRIC/MIST countries during 2015 were located in South Korea (National Institutes of Health, 2016).

The regulatory framework governing clinical trials is both well established and highly efficient, with the Ministry of Food and Drug Safety delivering CTA approvals inside 30 days where applications are deemed complete (PharmaVoice, 2015). The government has also played a key role in the development of an extensive, high-quality trials network through the publicly funded Korea National Enterprise for Clinical Trials (KONECT). The network now comprises over a dozen specialist centers and a total of more than 150 trial sites across the country. The government has also invested significant amounts in a national drug development fund, and offers financial support to overseas trial sponsors conducting Phase III trials in South Korea (Khaleel, 2014).

Regulators issued a total of 675 clinical trial approvals in 2015 – up from 652 in 2014 and almost 50% higher than the 2010 total. Trials being conducted by multinationals accounted for 291, or 45%, of the 2014 total, while two-thirds of multinational trials involved Phase III studies (KONECT, 2016).
TURKEY: NEW RULES AIM TO REDUCE CTA APPROVAL TIMES

The regulatory framework in Turkey has been overhauled progressively in a bid to align national rules with EU norms. Regulations governing clinical research have been harmonized as part of that process, and are now broadly similar to those contained in EU directives. Administrative changes have also been implemented in order to reduce trial approval times – partly by enabling the simultaneous submission of trial protocols to both local ethics committees and national authorities. That measure was part of changes introduced under new regulations published during April 2013, which also allow for protocols to be reviewed by ethics committees other than those within the institution at which a trial is to take place (Mene et al., 2013).

Bibliography


DRUG REGISTRATION

Long-term trends show a dramatic decline in the scale of drug lag times in emerging markets over the past four decades. This is almost exclusively the result of earlier submissions by originators, for which the BRIC/MIST countries (Brazil, Russia, India, China, Mexico, Indonesia, South Korea, and Turkey) and other emerging pharmaceutical markets represent increasingly attractive commercial targets. By contrast, the time taken to review New Drug Applications in these countries has increased as regulatory frameworks have been tightened (Wileman and Mishra, 2010). More recently, review times have remained stubbornly high in most BRIC/MIST markets, and have lengthened further in some (notably China). The registration process continues to act as a significant barrier to new drug approvals in these countries.

Registration is a significant barrier to market access

Poorly drafted and/or ambiguous regulations, the limited nature of regulatory expertise and resources, and the retention or imposition of barriers to the registration of imported drugs are among common problems encountered by originators attempting to access emerging markets.

Where locally manufactured generics represent an important source of affordable medicines for patients and publicly funded health programs, policymakers have often been reluctant to implement internationally accepted regulatory norms for fear of damaging domestic industry supply capabilities. Where these have been introduced, enforcement is often lax, handing some local producers an advantage over competitors that have invested in compliance with such standards.

Good manufacturing practice (GMP) standards are a prominent example of this two-tier approach, with regulators often much keener to police compliance where imported drugs are concerned. In countries that are not part of the international Pharmaceutical Inspection Co-operation Scheme (PIC/S), and that have not established bilateral mutual recognition agreements covering GMP, foreign plant inspections can cause lengthy delays in the approval of imported drugs. The problem has been mitigated in Mexico by a willingness on the part of regulators there to recognize foreign GMP certificates, but it remains a major issue for importers targeting the Turkish market.

Agencies charged with the registration of new drugs in emerging markets typically possess very modest resource bases. They employ a limited number of staff, and often struggle to recruit in-house reviewers with the technical knowledge required to assess complex dossiers. These agencies may once have had the capacity to manage relatively modest workloads. More recently, they have struggled to cope with dramatic increases in the number of applications being submitted by manufacturers keen to cash in on growing commercial opportunities.

Local plant requirements are a thing of the past in most BRIC/MIST markets, but still act as a hindrance to foreign companies operating in Indonesia. Regulations there have been relaxed, allowing companies that carry out primary packaging to qualify as local manufacturers, but those without packaging plants must enter into agreements with local partners in order to register their products.
Efforts to expedite drug registration are under way

Responding to pressure imposed by manufacturers, trading partners, and, importantly, local stakeholders demanding earlier access to innovative new drugs, regulators are pursuing efforts to improve the efficiency of existing registration procedures. Most agencies have either introduced electronic submission and review procedures, or have signaled their intention to do so. Existing regulations have also been overhauled in a bid to render submission and review procedures more efficient and transparent. Explicit deadlines for the completion of reviews have also been established or, as in Russia, reduced, while some agencies, including the China Food and Drug Administration (CFDA), have taken steps to discourage the submission of multiple generic applications. These have already seen user fees hiked sharply, but appear likely to include further developments, potentially including the outright rejection of applications for drugs already available from multiple sources (Bird & Bird, 2015).

Medicines agency budgets in several BRIC/MIST markets have been ramped up, enabling them to hire more staff and/or pay for the services of external experts. Again, the most dramatic developments are being witnessed in China, where the CFDA plans to employ more than 1,000 reviewers by the end of this decade (CIRS, 2015).

However, regulatory reforms have not always delivered the anticipated results. Indeed, in China and Russia, such reforms have created major new bottlenecks in the drug approval process. In both cases, changes to local clinical trial requirements were the cause. Regulators in both countries are now pursuing measures designed to address the unintended consequences of these reforms, but their impact will continue to be felt by applicants in the near future.

Where onerous clinical data requirements and lengthy review procedures have limited or delayed access to innovative new drugs, efforts are now being made to expedite their development and registration. This is being encouraged variously through the grant of local clinical trial waivers and the establishment of explicit fast track approval pathways, although access to these remains highly variable. While such measures are limited to orphan drugs in some countries, they are being made available significantly more broadly in others, including in China.

Key national developments

BRAZIL: "STRATEGICALLY IMPORTANT" DRUGS PRIORITIZED, OTHERS ENDURE LENGTHY WAITS

Brazil’s National Health Surveillance Agency (ANVISA; Agência Nacional de Vigilância Sanitária) has failed comprehensively to meet targeted deadlines for the review of dossiers submitted in support of new drug registrations. Efforts to reduce average approval time have seen the agency hire almost 300 new technicians, introduce electronic submission and review systems, and hike user fees in a bid to discourage multiple applications for the approval of generic copies (PhRMA, 2016). There is still no explicit fast track approval procedure for innovative new drugs in Brazil, however, and products with the potential to relieve pressure on public health budgets remain the most likely beneficiaries of priority reviews.
ANVISA enjoys an exceptionally broad remit. As well as administering regulations governing the development, manufacture, and sale of medicines, the agency plays a key role in the drug pricing process. It also scrutinizes pharmaceutical patent applications before they are reviewed in detail by Brazil's national patent office, and regulates food, cosmetics, and pesticides, as well as drugs and medical devices.

Existing regulations require ANVISA to complete its review of applications for the approval of new drugs and generics within 90 days, and for "similares" (branded copies) within 120 days. In fact, average approval times for innovative new drugs increased twofold during the early part of this decade, reaching 16 months by the middle of 2012 (BMI, 2012). Regulatory delays faced by importers are often compounded by the need to obtain ANVISA GMP certification before a request for marketing approval may be submitted.

Products deemed strategically important to the national healthcare system are reviewed on a priority basis, and are often completed in less than one year. The criteria used to determine strategic importance remain unclear, although in practice priority is often given to products with the potential to limit public sector drug spending. These include generics and products that are the subject of technology transfer agreements designed to pave the way for the local manufacture of drugs currently supplied via import (de Medeiros Rocha, 2013).

Innovative new drugs, including a number of cancer medicines, have also been approved on a priority basis, but Datamonitor Healthcare's analysis of US Food and Drug Administration (FDA) approval dates indicates that the registration of new oncology drugs in Brazil continues to lag behind FDA approvals by an average of around two years. Two of eight new cancer products registered by ANVISA since September 2014 received approval in Brazil approximately three years after they were granted marketing authorization in the US (see table below).
Novel hepatitis C treatments have fared better. Gilead’s Sovaldi (sofosbuvir) and Janssen’s Olysio (simeprevir) were both registered in Brazil approximately 14 months after receipt of their respective FDA approvals. The lag time for AbbVie’s combination product, Viekira Pak (paritaprevir/ritonavir/ombitasvir + dasabuvir), was just four months, while ANVISA registered Bristol-Myers Squibb’s Daklinza (daclatasvir) around six months before it was approved in the US (ANVISA, 2016; Drugs.com, 2016).

There is no explicit fast track approval process for innovative new drugs targeting life-threatening diseases. Compassionate use provisions – through which patients may access unregistered drugs for the treatment of such conditions where no existing treatment is available – have been relaxed, but these are still approved on a case-by-case basis (de Medeiros Rocha, 2013).

RUSSIA: REVIEW TIMELINES CUT; REGIONAL HARMONIZATION IN THE OFFING

Russian policymakers have moved to address market access issues triggered by the introduction of the country’s 2010 Law on the Circulation of Medicines. New drug approval timelines have also been trimmed, while the establishment of harmonized registration requirements under the Eurasian Economic Union (EAEU) initiative could benefit originators targeting Russia and some neighboring markets in the Commonwealth of Independent States.
Streamlining the drug approval process was among the main goals of the 2010 law, which overhauled rules governing the registration, import, export, and sale of medicines. In a bid to achieve that goal, it aimed to rationalize registration procedures, introduce more direct accountability, and establish explicit timelines for completion of the review process. Maximum overall review periods were set at 90 days for generics and 210 days for new drugs (Sheftelevich and Tripathi, 2010).

In practice, the state agency responsible for issuing registration certificates – Roszdravnadzor – has struggled to meet these targets, while new clinical trial requirements laid down in the law have emerged as a major barrier to market access for innovative medicines in Russia. Steps to resolve issues surrounding local clinical data requirements have now been taken, while deadlines for the review of new drugs have been cut (Gorodissky & Partners, 2015).

A package of measures designed to resolve problems created by the 2010 law was approved in December 2014. Some were implemented during 2015, while others will take effect in 2016 and 2017. In July 2015, the maximum review period for new drugs was cut from 210 days to 160 days from the date on which regulators acknowledge their acceptance of an application. Shorter deadlines (80 days) apply to the review of products eligible for fast track approval (including orphan drugs and pediatric medicines, as well as early generic entrants). Significantly, foreign trial data are now also sufficient to secure the approval of orphan drugs (EY, 2015).

The establishment of harmonized regulatory and registration requirements within the EAEU, scheduled for 2016, could enable applicants to obtain registrations in Armenia, Belarus, Kazakhstan, and Kyrgyzstan, as well as in Russia, through the submission of a single, harmonized dossier. Draft rules governing the examination and registration of pharmaceuticals were published by the Eurasian Economic Commission in the final quarter of 2015. Given the size and structure of other markets in the region, opportunities presented by the establishment of the EAEU will be of greatest interest to generics manufacturers. Nevertheless, dual access to markets in Russia and Kazakhstan may be of interest to originators.

INDIA: ORIGINATOR ACTIVITY DWINDLES AS IP PROTECTION AND CLINICAL RESEARCH CLIMATES DETERIORATE

Experience has shown that many new drugs launched in India face generic competition within a year, while the risks posed by new clinical trial liability regulations have also emerged as a further deterrent to launch activity (PhRMA, 2016). Until these are amended, few companies will pursue the registration of new drugs unless they are the subject of local trial waivers issued by the Central Drugs Standard Control Organization (CDSCO).

Where local trial requirements are waived, registration can be complete within 12–15 months, although it can often take an additional three months for foreign companies to secure import licenses. There is no formal priority review system. Instead, the CDSCO assesses applications on a case-by-case basis, with issues such as therapeutic efficacy and unmet need determining the outcome of requests for priority review (APAC, 2014).
Bayer’s colorectal cancer drug Stivarga (regorafenib) and Pfizer’s advanced renal cell carcinoma product Inlyta (axitinib) were approved by regulators in 2014, around two years after their respective US approvals. Since then, while the CDSCO has approved additional indications, strengths, and dosage forms for a number of established cancer drugs, its listings indicate that the organization has not approved any further oncology products containing a molecule new to the Indian market (CDSCO, 2015, 2016a).

While they remain rare, local clinical trial waivers were issued by the CDSCO in November 2015 for two novel hepatitis C drugs (Gilead’s sofosbuvir/ledipasvir combination product and Bristol-Myers Squibb’s daclatasvir). Gilead has signed agreements with 11 Indian manufacturers allowing them to develop and market generic sofosbuvir and sofosbuvir/ledipasvir combination products for use in 101 developing countries (Gilead, 2015). The agreement covers India and Indonesia, but excludes the six remaining BRIC/MIST markets.

In a bid to encourage the launch of more drugs for the treatment of rare diseases, the Drug Controller General of India has held discussions with the industry (CDSCO, 2016b). These have raised the prospect that a fast track approval pathway may be made available for orphan drugs, and that products awarded orphan status may be exempt from price controls administered by the National Pharmaceutical Pricing Authority.

**MANUFACTURERS CHALLENGE FDC BAN**

Fixed-dose combination (FDC) products have been registered in their thousands by manufacturers in India, both by originators as well as by domestic companies. Concern surrounding the safety and efficacy of some FDC products registered by state-level regulators has been growing, however, and the CDSCO announced a ban on products containing 344 FDCs in March 2016 (Chemistry World, 2016).

The ban, which affected products with aggregate sales of around INR30.5bn ($450m), was the subject of immediate and multiple legal challenges (Economic Times, 2016). Less than a week after it was announced, both Pfizer and Abbott had obtained interim stays against bans on their respective antitussives, Corex and Phensedyl, which are among the best-selling brands in the Indian retail market (FiercePharma, 2016).

**CHINA: ALL CHANGE, AS REGULATORS EMBARK ON A MAJOR REFORM DRIVE**

Since the beginning of 2015, regulators in China have issued a stream of new rules designed to speed up the development and registration of new drugs. As well as encouraging domestic R&D and improvements in the quality of generics, these aim to transform the efficiency and transparency of new drug review and approval procedures, enabling the CFDA to clear a massive backlog and to cope more effectively with anticipated future workloads.

The CFDA and its Center for Drug Evaluation (CDE) were already struggling to deal with submission volumes, but the situation deteriorated sharply in 2014 when the backlog of drugs awaiting approval rose by one-third to more than 18,500 (Medical Daily, 2015). Median new drug approval times in China had already edged up towards two years in the early part of this decade. Coupled with lengthy
trial approval procedures, this had seen the emergence of a drug lag time averaging approximately five years (CIRS, 2015).

Some changes had already been introduced or were being piloted; the CFDA had implemented significant fee hikes designed to discourage multiple generic submissions, and had announced plans to hire hundreds of new reviewers by the end of this decade (CIRS, 2015). The catalyst for more substantive change was the publication in August 2015 of a State Council opinion on reform of the review and approval system for drugs and medical devices.

Draft regulations designed to implement changes called for by the council were published later in 2015 and in the early part of 2016, and some were finalized during the first quarter of 2016. Key developments will include (EFPIA, 2016):

- broader access to fast track and priority review procedures
- the introduction of a marketing authorization holder (MAH) system.
- the establishment of a new drug classification system for registration purposes.

Fast track approval will be available to a substantially broader range of products, including cancer and HIV treatments, pediatric drugs, and products that offer significant clinical improvements over existing available therapies. Priority review and approval procedures will apply for drugs offering improvements in the treatment of specific diseases or patient groups. Potential beneficiaries will include products for the treatment of cancer, HIV, tuberculosis, and viral hepatitis, and drugs indicated for use in rare, pediatric, or geriatric conditions. Both trial approval and dossier review procedures will be expedited for qualifying products.

The MAH system will be piloted in around a dozen provinces through the period to 2018, with a view to nationwide implementation thereafter. This will allow local manufacturers, research institutes, and individuals to file for approval of a drug, outsourcing production to third parties once a marketing authorization has been obtained (EFPIA, 2016).

For registration purposes, drugs will in future be placed in one of five categories. The first two will include innovative or "improved" drugs not previously marketed either in China or elsewhere. The third and fourth will include generics, while imported products – whether originators or generics – will be placed in a fifth group (EFPIA, 2016).

While these changes should help the CFDA tackle its existing backlog and review New Drug Applications more rapidly in the future, some rules require clarification, while others could actually disadvantage originators. The cause of most concern is the new drug classification system, which multinationals fear could prevent innovative products already approved or marketed outside China from accessing expedited review procedures. In turn, multinationals believe this could affect their ability to obtain effective exclusivity for original brands in China (PhRMA, 2016).
Originators have also called for the clarification of rules governing priority review and approval procedures. Specifically, they are keen to see the establishment of explicit review timelines for the priority review pathway, and the publication of further details on the waiver of local clinical trial requirements for qualifying products (EFPIA, 2016).

The impact of the reforms will also be dependent on the ability of the CFDA to deliver on pledges to increase CDE reviewer numbers, and to reduce the number of generic submissions received by the center. Fee hikes and other measures designed to deter multiple submissions appear to have had a relatively modest impact in 2015, when the CDE accepted 8,211 new registration applications – down by only 7% on the 2014 figure (EFPIA, 2016).

**MEXICO: RECOGNITION OF FOREIGN APPROVALS DRIVES UP NEW DRUG REGISTRATION ACTIVITY**

Significant improvements in the efficiency of the drug approval process in Mexico have been witnessed since 2011, when Mikel Arriola took over as head of the Federal Commission for the Protection against Sanitary Risk (COFEPRIS; Comisión Federal para la Protección contra Riesgos Sanitarios). Under his direction, the number of new drug approvals issued by COFEPRIS increased sharply as the agency began to streamline procedures and make more use of external reviewers. Equally significant for innovators was the decision to begin recognizing approvals already granted by regulators in the US and EU, as well as in a handful of other highly regulated markets (European Commission, 2015).

Having issued registrations for 136 new allopathic drugs in 2010, COFEPRIS approved more than 300 in 2011. Numbers fell back in the following two years, but the agency registered more than 300 new allopathic drugs in both 2014 and 2015. Most registrations are for generics, but innovative new drugs have featured more prominently since COFEPRIS began recognizing US and EU approvals (COFEPRIS, 2016).
Novel treatments for cancer, HIV, rheumatoid arthritis, and hepatitis C are among those registered over the past two years (COFEPRIS, 2016). In the hepatitis C treatment sector, Gilead endured a frustrating wait for approval of its sofosbuvir and sofosbuvir/ledipasvir products in Mexico. Both were finally registered by COFEPRIS during the first quarter of 2016, several months after approvals had been granted by the agency for competing products from AbbVie (Viekira Pak) and Bristol-Myers Squibb (Daklinza and Sunvepra).

Improvements delivered by COFEPRIS have been lauded by manufacturers (PhRMA, 2016). They have also been acknowledged by the Pan-American Health Authority (PAHO), which has granted it "regional reference agency" status (PAHO, 2012). This will deliver additional benefits for applicants, since registrations granted by COFEPRIS will also be recognized by some neighboring Latin American countries.

**INDONESIA: "FORCED LOCALIZATION" ADDS TO MULTINATIONAL CHALLENGES**

Poor levels of intellectual property protection, widespread counterfeiting of branded drugs, restrictive import regulations, and the modest nature of both public and private purchasing power all limit the appeal of Indonesia as a target for the registration of innovative new medicines.

Since the beginning of this decade, multinationals have faced an additional challenge posed by the Ministry of Health (MoH) Decree 2010, which effectively prevents foreign companies from obtaining marketing authorization for their products unless they either manufacture locally or employ the services of a domestic manufacturing partner. The definition of "local manufacture" was subsequently relaxed, enabling primary packaging facilities to qualify. Nevertheless, originators regard the provision...
as an unfair barrier to market access, and will continue to lobby for the complete removal of “forced localization” requirements (PhRMA, 2016).

Where multinationals do pursue the registration of new drugs, they continue to face burdensome regulatory delays (PhRMA, 2016). This is despite the fact that the National Agency of Drug and Food Control (NA–DFC; known more widely as BPOM [Badan Pengawas Obat dan Makanan]) is willing to accept foreign clinical trial data in support of most new drugs (JPMA, 2014).

On paper, BPOM registration timelines vary by product type, from 100 to 300 days. Orphan drugs and life-saving medicines qualify in theory for the 100-day procedure, but there is no explicit priority review system, and few reviews are completed within theoretical time limits (APAC, 2015).

BPOM appointed an additional 20 registration staff during 2015, and has committed to the provision of training initiatives in a bid to improve the efficiency of the review process (PhRMA, 2016). It has also begun to introduce electronic submission and review procedures (Paskalis, 2016). Both of these initiatives are designed primarily to help the agency to deal with a sharp increase in the number of generic applications, however. This has been triggered by rising demand for generics, which has been fueled by the rollout of Indonesia’s new national health insurance program. Early indications are that this has prompted a further shift away from branded medicines to the use of generic drugs (ISPOR, 2016).

With BPOM expected to maintain its focus on the registration of new generics in the near term, approval times for innovative new drugs will remain both lengthy and unpredictable. In the longer term, the Association of Southeast Asian Nations (ASEAN) regional trade initiative represents the most likely driver of improvements in the local drug registration climate. Like other national agencies within the trading bloc, BPOM already accepts applications submitted in ASEAN Common Technical Dossier format (APAC, 2015).

SOUTH KOREA: SAFETY CONCERNS DRIVING NEW REGULATORY REQUIREMENTS

South Korea’s Food and Drug Administration became the Ministry of Food and Drug Safety (MFDS) in 2013, as part of a reorganization designed primarily to address concerns surrounding the safety of food and drug products (Gaffney, 2013). Having been vested with ministerial status, the revamped agency now manages its own budget and has the power to draft new legislation governing pharmaceuticals.

In line with its drive to tighten drug safety, the MFDS began demanding the submission of Risk Evaluation and Mitigation Strategies in applications supporting the approval of new chemical entities (NCEs) and orphan drugs in 2015. Since 2013, authorizations have also been issued on a five-year, renewable basis. Drugs approved before that date will be subject to a rolling review program scheduled to begin in 2018 (APAC, 2015). This will increase the agency’s workload, and could have an adverse effect on approval timelines.

The MFDS works to a target review period of 160 days for NCEs. Longer deadlines apply where GMP
inspections are required, but these have become less frequent since South Korea became a member of the PIC/S in July 2014. In practice, the time taken to approve New Drug Applications averages approximately 12 months (APAC, 2014).

A priority review system exists for orphan drugs and new medicines targeting life-threatening or serious diseases. A new regulation on the designation of orphan drugs, issued in July 2015, listed 206 orphan products and a further seven development-stage orphan drugs. To qualify for orphan drug status under the new designation, a product must be indicated for the treatment of a condition that affects 20,000 or fewer patients in South Korea, and must meet a significant unmet clinical need. Existing drugs containing the same substance must generate annual sales of no more than $1.5m, or, where they are indicated for the treatment of diseases occurring in 500 or fewer patients, no more than $5m (MFDS, 2015).

TURKEY: GMP CERTIFICATION DELAYS FRUSTRATE ORIGINATORS

GMP inspection requirements continue to frustrate companies targeting the registration of new drugs in Turkey, adding significantly to average approval times. Some improvement has been witnessed since the early part of this decade, but the average time taken by the health ministry and the Turkish Pharmaceuticals and Medical Devices Agency to complete regulatory reviews still stands at 438 days, compared with a target time of 255 days. Delays in the registration of new drugs that do not qualify for priority GMP audits are often considerably longer (PhRMA, 2016).

The root of the problem lies with new drug registration rules implemented in 2009. These require the MoH to carry out an on-site GMP inspection of all foreign production facilities unless certification has been obtained from regulators in a country that recognizes Turkish GMP approvals. Since Turkey is not a member of the PIC/S initiative, this means ministry inspectors conduct on-site inspections of almost all overseas manufacturing facilities. Between December 2009 and April 2013, 93% of all GMP applications submitted by manufacturers were processed via on-site inspections. The mean time taken by regulators to complete the certification process during that period was 677 days (Gür Ali, 2013).

The MoH has since appointed more inspectors, and announced additional measures designed to address the problem during 2015. These have seen regulators begin to prioritize GMP audit procedures for highly innovative or life-saving products, in respect of which marketing application procedures may also run in parallel to the GMP approval process rather than beginning once GMP approval is complete. Separately, the expiration of some GMP inspection certificates has also been delayed (PhRMA, 2016).

However, originators say that these measures will not be sufficient to resolve the problem. There are even fears that, with regulatory resources being concentrated on priority applications, other new drugs could face even lengthier delays (PhRMA, 2016). Research-based companies have called on regulators to recognize GMP certificates accepted by their counterparts in the US, EU, and other PIC/S signatories, as they did before the introduction of the new registration rules in 2009.

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PRICING

The pricing of innovative medicines has been the subject of growing debate – even in the world’s richest economies, where costs associated with the reimbursement of new cancer drugs and, more recently, revolutionary hepatitis C treatments have stretched payer budgets. In low-income countries, where government drug budgets are much more limited, and where such products are beyond the pockets of all but a wealthy few patients, the issue poses more fundamental problems.

Improving patient access to subsidized medicines is a common goal across the BRIC/MIST markets (Brazil, Russia, India, China, Mexico, Indonesia, South Korea, and Turkey). This is being achieved largely through the provision of free or subsidized multi-source drugs, but patient organizations and other stakeholders are also pressing for access to newer-generation products that can transform prognoses for those with serious, life-threatening conditions.

For governments, which foot the vast majority of the subsidized medicines bill in most BRIC/MIST markets, this poses a major financial challenge. Governments in three of the eight countries have issued compulsory licenses for the import or local manufacture of one or more patented drugs. This is not feasible on a widespread basis, however, and other solutions are being considered. Chief among these are the introduction or reinforcement of regulatory controls on patented drug prices, the establishment of negotiated prices, and the use of bulk purchasing to lever discounts on costly products.

Since these strategies are designed primarily to curb public spending, regulatory controls have often been limited to products on either essential drugs lists (EDLs) or public sector reimbursement schedules. Prices in other segments of the market remain free from regulatory control in several BRIC/MIST markets.

Pricing controls are a growing feature of the BRIC/MIST landscape

INTERNATIONAL REFERENCING

Cross-country referencing has been adopted widely by governments as a means of limiting new drug launch prices. The approach is an increasingly widespread feature of both developed and emerging markets, but is often particularly restrictive in low-income countries. Low launch prices are generally achieved through the choice of reference markets and/or the mechanism used to set local limits on launch prices.

Brazil, Russia, and Turkey have all set maximum launch prices for innovative new drugs via reference to ex-manufacturer prices prevailing in a basket of overseas markets. While the list of markets referenced by Brazil includes the US, its presence is essentially irrelevant since Brazilian launch prices may not exceed the lowest price prevailing in any market on the list. Similar benchmarks are applied by regulators in Turkey, and in Russia, where the list of reference countries has recently been updated. This involved the removal of Germany and Switzerland from the list, with those two countries replaced by the lower-priced European markets of Hungary and Croatia.
Elsewhere, a reference country list is being used by regulators in China, where the first nationally negotiated prices for patented brands have recently been agreed, and in Mexico, where the price of patented drugs and other single-source medicines sold into the institutional market has been capped since 2008.

So long as they do not feature on the country’s EDL, patented drug prices are currently free from explicit regulatory control in India. The imposition of patented drug price controls has been under discussion for several years, however, and international referencing is expected to feature if new rules are eventually imposed.

OTHER PRICING CONTROL MECHANISMS

Governments employ a range of other tools to limit the prices paid by hospitals and other public sector purchasing agencies for new drugs. Bulk tendering is the most widespread example, but compulsory discounts are also imposed on public sector purchases in Brazil and Turkey, while more sophisticated mechanisms are beginning to feature in countries where the provision of high-cost drugs is being subsidized by governments.

Price-volume agreements (PVAs) are an established feature of the pricing landscape for new drugs seeking access to South Korea’s reimbursement list. Regulators there have also begun to strike risk-sharing agreements designed to limit the exposure of South Korea’s national health insurance (NHI) fund to costs generated by the use of some innovative, costly medicines. Risk-sharing deals have also been struck by the government in Indonesia in a bid to improve patient access to new drugs.

Less conventional means have been used by some governments to limit innovative drug prices. In Turkey, this has involved the use of artificially low fixed exchange rates to set drug prices, which originators say cost them around $5bn between 2009 and 2015, when the policy was finally relaxed (PhRMA, 2016).

Manufacturers are refining pricing strategies

New drug prices are generally free from regulatory control where governments have not committed to fund their provision, either partially or in full. Demand for original brands in the private sector of most BRIC/MIST markets is limited, however, reflecting low patient incomes, the limited reach of private health insurance, and the absence of outpatient drug benefits from most private plans. Demand is particularly limited for innovative new drugs that carry hefty price tags.

A desire to preserve global list prices and fears surrounding the leakage of cheaper drugs into other markets have traditionally prevented originators from adopting more nuanced pricing strategies in low-income countries. This situation has begun to change, however – partly because multinationals themselves have adopted a more flexible approach, but also because governments in some markets have adopted mechanisms that enable originators to sell into institutional markets at lower prices without compromising list prices.

Moves towards the adoption of more flexible pricing strategies in low-income markets began to
emerge around a decade ago. Merck & Co was at the vanguard of this trend, launching diabetes drug Januvia (sitagliptin) at one-fifth of the product’s US price in India (The Economic Times, 2009). GlaxoSmithKline soon followed suit, announcing sharp cuts in the price of its patented products in the world’s least developed countries (LDCs). While none of the eight BRIC/MIST countries feature on the list of LDCs, the company said it would also adopt more flexible approaches to pricing in markets such as India (The Guardian, 2009).

The success of Januvia, as well as Merck’s sitagliptin + metformin combination product Janumet, in India encouraged other manufacturers to begin experimenting with country-specific prices, while other strategies designed to make original brands more affordable to a larger proportion of patients in low-income countries have also been established. These include the establishment of flexible patient payment initiatives, patient voucher schemes, and tiered pricing models.

Voucher schemes enable patients to purchase original brands at discounted prices, while tiered pricing initiatives involve the direct correlation of prices charged to individual patients with their income. Eisai adopted a tiered pricing model for its breast cancer drug, Halaven (eribulin), following its launch in India during 2013. High-income patients are charged the full price, but those on middle incomes are able to purchase the product at reduced rates, while Eisai funds free provision of Halaven to the country’s poorest patients (Eisai, 2013). Announcing plans to launch two new cancer drugs in India during 2015, Boehringer Ingelheim said it was considering a range of flexible pricing options, including staggered payments and a differential (income-based) pricing model (The Economic Times, 2015).

Packaging and labeling changes have been implemented by manufacturers operating country-specific pricing strategies in a bid to prevent the subsequent re-export of products purchased at low prices. Tiered pricing initiatives pose additional problems, including the potential resale of drugs acquired at little or no cost by patients in low-income groups. Building relationships with prescribers and distributors can help to minimize the risk of such leakage, but this is a challenging proposition in large, complex markets such as India and China.

**Pricing policy trends**

Regulatory pricing controls are being stepped up in countries where governments are subsidizing a growing share of overall drug costs, or have announced plans to do so. Generally, rates of change in pharmaceutical coverage determine the pace and extent of pricing reforms. Accordingly, some of the most fundamental (and problematic) reforms encountered by manufacturers in recent years have been implemented in Turkey, where the government has taken on much broader responsibility for healthcare provision and funding.

Elsewhere, major changes are being implemented in China, where new pricing rules will have a fundamental impact not only on new drug prices but also on those of older original brands and generics. Substantive pricing reforms are also expected to accompany the establishment of a universal outpatient drug benefits scheme in Russia. Financial issues appear certain to delay the rollout of that initiative, however, and its full impact on pricing policy may not become clear for several years.
While tighter pricing controls are generally being imposed as governments foot a growing proportion of the drug spending bill, India is a notable exception. There, successive governments have failed to deliver on expansive health insurance coverage pledges, leaving most patients to foot the vast majority of their pharmaceutical costs. Nevertheless, a shift towards more widespread regulatory control of drug prices has been witnessed since 2012, and the imposition of additional measures – possibly including explicit controls on patented drug prices – is being discussed.

Key national developments

BRAZIL: MARKET-WIDE PRICE HIKES OFFER SOME RELIEF FOR ORIGINATORS

Research-based manufacturers, which have seen the real post-launch prices of many original brands eroded progressively by regulatory controls, were offered some relief in March 2016 when the Brazilian government’s Drug Market Regulation Chamber (CMED; Câmara de Regulação do Mercado de Medicamentos) sanctioned market-wide price hikes of up to 12.5%. With the consumer price index having risen by 10.4% over the preceding 12 months, increases will do little more than offset inflation (Gestão Farma, 2016). Nevertheless, this will still represent a considerable improvement for originators, which have borne the brunt of more restrictive caps on annual price growth in recent years.

Until 2015, CMED imposed differential caps on annual price hikes, in accordance with levels of generic penetration in individual market segments. In 2014, products in therapeutic classes where generics accounted for more than 20% of sales by value were handed an annual increase of up to 5.68%. Those in classes where generics accounted for 15–20% of sales by value were permitted to raise prices by up to 3.35%, but hikes of just 1.02% were sanctioned for products in classes where generic penetration was less than 15%. With inflation running at more than 6%, that meant the real prices of many original brands declined sharply (IHS Markit, 2014).

In 2015, CMED used levels of concentration in specific market segments to calculate permitted price rises, which were sanctioned at less widely differentiated rates, ranging from 7.7% to 5.0% (IHS Markit, 2016). The implementation of a single, market-wide cap on price growth in 2016 represents a further welcome change for originators, although it remains unclear whether this harmonized approach will be retained in the long term.

SATISFACTORY LAUNCH PRICES ARE STILL DIFFICULT TO ACHIEVE

Caps on post-launch price growth mean the ability of manufacturers to obtain satisfactory launch prices for new drugs is critical. This has proved difficult, however, with CMED presiding over a similarly restrictive approach to the establishment of maximum prices for new drugs. This has entailed the imposition of caps at both ex-manufacturer and public price levels.

For new drugs, the ability of applicants to demonstrate clear efficacy, safety, or cost benefits over existing treatments remains the key to achieving satisfactory launch prices. Only where such benefits are acknowledged by CMED is a new drug granted category I pricing status. Then, launch prices are benchmarked against those in nine other markets (Australia, Canada, France, Greece, Italy, New...
Zealand, Portugal, Spain, and the US). Ex-manufacturer launch prices in Brazil may not exceed the lowest price prevailing in the nine reference countries (Eye for Pharma, 2013).

New drugs that fail to demonstrate clear efficacy, safety, or cost benefits are consigned to category II (effectively "me-too") status. The launch price of these products may not exceed the price of an existing therapeutically equivalent product selected by CMED. Since the difference between prices approved for category I and category II products is often dramatic, originators have appealed a number of initial CMED categorization decisions.

Even where new drugs are granted category I status, approved launch prices are often lower than those requested by manufacturers. Just 14 of 433 new drugs approved by the National Health Surveillance Agency (Agência Nacional de Vigilância Sanitária) between March 2004 and December 2011 were granted category I status. On average, maximum launch prices approved by CMED for those products were 19% lower than prices requested by applicants (The Pharma Letter, 2013).

RUSSIA: NEW EDL PRICE RULES MAINTAIN ADVANTAGE FOR LOCALLY MANUFACTURED DRUGS

Products not contained on Russia’s EDL are free from regulatory control, but originators still find it difficult to achieve satisfactory launch prices or obtain subsequent price increases for imported products that feature on the list.

Rules governing the registration and update of EDL drug prices, which are subject to caps set at ex-manufacturer level, were updated in October 2015. The changes will do little to ease existing problems faced by imported products, however, and will continue to hand significant advantages to manufacturers located in Russia or other Eurasian Economic Union member states.

Maximum ex-manufacturer prices (MMPs) must be registered for all drugs before they are included in the EDL. Foreign companies seeking the inclusion of a new drug must provide regulators with more detailed information than their domestic counterparts, including data on the ex-manufacturer price of the product in a basket of around 20 foreign countries. The MMP of an imported drug may not exceed the lowest ex-manufacturer price in any of these reference markets. Changes in October 2015 saw Hungary and Croatia replace Germany and Switzerland in the reference country basket, which is now dominated by low-priced European markets (PwC, 2015).

In theory, companies may re-register the prices of products already on the EDL annually. In practice, however, while locally manufactured drugs have again been granted some leeway, foreign products on the list have been subject to a virtual price freeze since the beginning of this decade. The new EDL pricing rules do make explicit provision for the re-registration of imported drugs, but restrictive qualification criteria mean significant increases will be difficult to achieve in practice, not least because prices must remain below those in any of the reference countries (PwC, 2015).

More fundamental pricing reforms are likely to accompany the eventual rollout of a comprehensive outpatient drug reimbursement scheme. Regulators have discussed the introduction of generic reference pricing for multi-source drugs and the possible negotiation of prices for patented brands
and other single-source products. Originators prepared to offer significant ground on price could be rewarded with substantially increased volumes under such a scheme, although their willingness to negotiate will depend on the scale of funding for the provision of outpatient drug reimbursement.

INDIA: DPCO BROADENED, PATENTED DRUG PRICING CONTROLS STILL ON THE AGENDA

The number of drugs subject to direct pricing control in India has increased sharply since 2013, while the imposition of controls on the price of patented drugs, which has been the subject of debate for almost a decade, remains under active discussion. In a market where original brands lacking patent protection can enjoy lengthy lifecycles, both of these issues have implications for originator market access strategies.

Moves towards the expansion of regulatory pricing controls were triggered by the adoption of a new National Pharmaceutical Pricing Policy in 2012. This prompted both a change in methods used to calculate caps on the price of products subject to the country’s Drug Price Control Order (DPCO) and a significant increase in the number of products affected by the caps (Reuters, 2012).

Ceilings are now calculated by averaging the prices of all brands with a market share of at least 1%. Having previously applied to only 74 molecules, these have been calculated since 2013 for all products on the country’s National List of Essential Medicines (NLEM). From 2013, this meant that products containing 348 molecules were affected (Reuters, 2012).

In July 2014, the National Pharmaceutical Pricing Authority (NPPA) announced the imposition of caps on around 100 cardiovascular and diabetes drugs that did not feature on the 2013 NLEM. The move prompted a legal challenge by manufacturers, which averted the imposition of more ad hoc caps, but which failed to secure the removal of ceilings on products affected by the 2014 announcement (Livemint, 2014).

A new, revised and expanded version of the NLEM was adopted in December 2015. Around 70 drugs were removed from the existing list, while more than 100 new molecules were added. The net result was a further increase, to 376, in the number of drugs on the list, and therefore subject to DPCO price caps. High-profile additions to the 2015 list included oncology drugs (notably gefitinib, rituximab, and trastuzumab), the diabetes treatment glimepiride, and around a dozen antivirals, including hepatitis C drugs such as sofosbuvir (Scrip, 2015a). In March 2016, the NPPA published an amendment to the DPCO that will trigger the imposition of price caps for all products added to the NLEM in 2015 (The Pharma Letter, 2016).

The NPPA monitors the price of products not subject to the DPCO control mechanism, including patented brands, and may intervene where it finds that manufacturers have implemented unreasonable price hikes. It has done so on a regular basis, but has struggled to enforce payback requirements that are triggered where companies are found to have pursued unreasonable pricing policies.

The potential imposition of direct controls on the price of patented brands has been discussed for
around a decade now, but no concrete action has been taken to date. Early proposals to reference prices in a basket of overseas markets, adjusting Indian prices to take account of differences in per capita income, were ditched in the face of strong industry opposition, and an inter-ministerial group was set up to address the issue in 2014. While it has yet to table a full report, there have been continued calls in some quarters for the imposition of regulatory controls on the price of all drugs, including patented brands. A 2015 report by parliament’s standing committee on chemicals and fertilizers, which called for the imposition of market-wide regulations, said the availability of life-saving drugs at reasonable prices should be a particular priority (RAPS, 2015).

The expansion of the DPCO mechanism has seen price caps imposed on a number of original brands. These triggered relatively modest cuts for some products, however, while others have seen volumes rise sharply in the wake of more substantial reductions. Cuts in the price of several antiretrovirals averaged approximately 3%, for example, with the price of sofosbuvir reduced by 2.7% (The Times of India, 2016). Adjustments in the price of DPCO products, which are sanctioned on an annual basis at rates in line with wholesale price index movements, have also helped to drive value growth for affected brands. As a result, most multinationals have escaped the hit they feared would be delivered by the expansion of DPCO pricing controls.

Coupled with these relatively positive early outcomes, a desire to avoid the imposition of direct controls on patented brands could encourage multinationals to adopt more flexible pricing strategies. Companies such as Merck & Co, which pioneered India-specific pricing with Januvia, have already shown that flexible approaches can pay dividends, while Boehringer Ingelheim, which is readying the launch of two new cancer drugs in India, is also mulling the pursuit of innovative approaches to pricing.

**CHINA: ORIGINATORS NEGOTIATE FIRST NATIONAL PRICING DEALS**

A major shift in drug pricing policy – from a regulated pricing environment to a market-driven system – was implemented by the authorities in China at the beginning of June 2015 (Pharma Times, 2015). For patented brands and other single-source drugs, this will involve the negotiation of prices at national level. Standard reimbursement prices will be set for drugs reimbursed under government-run health insurance schemes but, with the exception of narcotics, psychotropics, and some centrally procured products such as vaccines, manufacturers will be free to set the price of other products. Additionally, as a result of other changes, originators will no longer be able to charge premium prices for patent-expired brands. Instead, these products will be forced to compete directly on price with generics (Covington & Burling, 2015).

Previously, while they were required to register prices with the National Development and Reform Commission (NDRC), originators were free to set their own prices for patented medicines. The NDRC set maximum retail prices for fully reimbursed drugs, while provincial pricing authorities played a key role in the establishment of partially reimbursed drug prices. But in a market where around three-quarters of all prescription drug sales are generated in public hospitals, and where hospital supplies are dominated by provincial tenders, actual transaction prices often bore little relation to the theoretical maximum retail prices set by the NDRC. This was the case for many patented brands as
well as for multi-source drugs, with originators often trading price in return for access to provincial
drug formularies and reimbursement lists.

The introduction of nationally negotiated prices for patented brands is designed to drive down the
price of such products. In theory, resulting prices will apply across the country, ruling out the need for
manufacturers to negotiate pricing terms with individual provinces or hospitals. It remains to be seen
whether this will be the case in practice, however, and since the establishment of national prices will
not guarantee access to reimbursement lists, some originators may be reluctant to participate in the
process.

Nor, while the first nationally negotiated pricing agreements have already been announced, is it clear
exactly how the process is conducted, or what factors are taken into account. International
benchmarking will play a role, however, with regulators requesting information from manufacturers
on prices in a list of 15 other countries, including Hong Kong and Taiwan.

PRICING DEALS ANNOUNCED FOR VIREAD, IRESSA, AND CONMANA

The National Health and Family Planning Commission (NHFPC) began discussing potential
negotiations on the price of patented drugs with more than two dozen manufacturers during the final
quarter of 2015. This led to detailed discussions with five companies and, in May 2016, an
announcement by the commission that it had secured substantial cuts in the prices of three patented
brands. The products involved, and price cuts negotiated, were as follows (Fierce Pharma, 2016):

- GlaxoSmithKline agreed to cut the price of its hepatitis B drug, Viread (tenofovir), by 67%.

- AstraZeneca agreed to cut the price of its lung cancer drug, Iressa (gefitinib), by 55%.

- Local company Zhejiang Beta Pharma agreed to cut the price of its lung cancer drug, Conmana
  (icotinib), by 54%.

Announcing the agreements, the NHFPC said the new, lower prices would apply to all public health
institutions. The commission said it expected the cuts to trigger reductions in the prices of other
patented products with similar indications. Significantly, in a later statement, it said the three
manufacturers had agreed to lower prices "on condition of bulk purchase" (NHFPC, 2016). This would
appear to indicate that, in return for cutting prices, companies were offered some form of
commitment where purchasing volumes are concerned.

The promise of volume guarantees is expected to encourage more originators to enter into national
pricing negotiations for patented brands. Not all will result in the establishment of agreed prices,
however, as evidenced by the outcome of early negotiations. For while GlaxoSmithKline, AstraZeneca,
and Zhejiang Beta Pharma agreed to cut the prices of their respective brands, no agreement was
reached with Roche on a reduction in the price of its erlotinib-based cancer drug, Tarceva, while the
outcome of negotiations with Celgene on a fifth, unidentified product remains unclear (The Wall
MEXICO: PRIVATE SECTOR PRICES SET TO REMAIN FREE FROM REGULATORY CONTROL

Prices in the private sector of the Mexican pharmaceutical market are subject to theoretical controls. These are lax, however, and compliance is, in effect, entirely voluntary. The imposition of stricter limits remains highly unlikely, given the implications that significant cross-border price differentials could have on parallel trade between Mexico and the US.

Institutional market prices are subject to caps established by a commission set up in 2008 to negotiate the price of drugs and other health inputs purchased by public institutions (CCNPMIS; Comisión Coordinadora para la Negociación de Precios de Medicamentos y otros Insumos para la Salud). Actual purchase prices in the public sector are still determined largely through competitive tendering. Nevertheless, the establishment of transparent ceiling prices has had a significant impact in a market where individual institutions previously purchased patented drugs at widely varying prices.

Between 2008 and 2010, the CCNPMIS negotiated caps on the prices of more than 150 patented drugs, including antiretrovirals and products for the treatment of serious diseases such as cancer and diabetes. In 2009 alone, these generated reported savings of approximately MXN5bn ($325m), while cumulative savings over the three-year period from 2009 to 2011 were MXN11.6bn ($731m) (SSA, 2011). Since 2012, the CCNPMIS has imposed ceilings on the prices of all single-source drugs purchased for use in the public sector.

INDONESIA: INDIVIDUAL NEGOTIATIONS ARE BEING UNDERTAKEN FOR PUBLIC SUPPLY OF INNOVATIVE DRUGS

Although prescription drugs are still free from explicit regulatory control in Indonesia, pressure on prices in the rapidly expanding institutional market is being stepped up in a bid to stabilize NHI scheme finances. For multi-source drugs, this is being achieved primarily through the use of electronic tendering. Funding the provision of single-source originator products, including patented brands, poses a much bigger challenge for the government as it attempts to complete the rollout of an NHI scheme (known as the JKN; Jaminan Kesehatan Nasional).

In the absence of explicit regulatory controls, originators will be reluctant to compromise on the list price of brands sold into the private sector, where rising incomes and the emergence of a growing private hospital and clinic market have increased opportunities in recent years. Acknowledging that fact, but with limited funds to support the provision of costly original brands, the Ministry of Health has conducted negotiations with individual manufacturers for the supply of single-source products listed on the JKN drug formulary. Risk-sharing agreements have been struck for the supply of some innovative drugs (ISPOR, 2016).

While involvement in the emerging JKN market makes long-term strategic appeal, most multinationals will continue to focus on opportunities in the private sector for the foreseeable future. There, flexible approaches to pricing will also pay dividends, helping to generate prescriptions and obtain listings on hospital and payer formularies.

SOUTH KOREA: POLICYMAKERS TO MAINTAIN TIGHT GRIP ON ORIGINATOR PRICES
While originators may win some modest concessions, policymakers in South Korea will be determined to maintain a tight grip on costs associated with the reimbursement of innovative new drugs. Multinationals complain that new drugs achieve low introductory prices, which are subsequently eroded by frequent price cuts. PVAs can also trigger substantial cuts in the prices of original brands where they generate reimbursement spending in excess of anticipated levels.

The country’s NHI scheme provides much broader access to subsidized medicines than programs in most other BRIC/MIST markets. Accordingly, more sophisticated measures designed to limit NHI drug spending have been established. These include comprehensive pricing and reimbursement regulations, which resemble those in most developed pharmaceutical markets, and which have been the subject of frequent revision over the past 10 years.

Introductory prices for new drugs seeking access to the NHI reimbursement list are the subject of negotiations between applicants and regulators. While the process involves a pharmacoeconomic evaluation, prices are set via reference to the weighted average price of existing products in a therapeutic class. The imposition of regular, discount-based price cuts on NHI-listed products means most comparators will have seen their prices eroded, limiting launch prices achieved by subsequent arrivals (PhRMA, 2016).

The launch price of new drugs added to the NHI reimbursement list between 2004 and 2013 was less than half the OECD average, while a 2014 comparison of 36 patented products found that ex-factory list prices in South Korea were lower than those in any of 10 other Asian markets, including China and Indonesia (KRPIA, 2014).
Post-launch prices are cut on a regular basis. Reductions are based on the difference between reimbursement prices and actual transaction prices (ATPs), which is ascertained through regular market monitoring, and which results in annual price adjustments for most reimbursed drugs. Since 2014, hospitals and pharmacies have been permitted to retain a proportion of the discounts they negotiate with suppliers, encouraging them to pursue a more aggressive stance in negotiations. Ignoring calls from manufacturers to delay the imposition of initial cuts under the new regime, the government reduced the prices of more than 4,000 products by an average of just over 1% in March 2016 (PhRMA, 2016).

PVAs can also trigger post-launch price cuts, and recent reforms again threaten to exacerbate their impact on originator prices. Prices may be cut by up to 10% if reimbursement spending generated by a product exceeds a defined threshold and has increased by 10% or more in the course of a single year. The thresholds at which cuts are triggered was raised in 2015, but these now apply to all strengths of a product, while higher spending on new reimbursed indications may also result in re-pricing (PhRMA, 2016).

Manufacturers have called on policymakers to reduce the frequency of ATP price cuts (from once a year to once every three years), and have lobbied for the establishment of new reimbursement pricing procedures that offer more adequate rewards for innovation. Some changes have been implemented.
since the beginning of 2015, but multinationals say these will offer little improvement for foreign companies operating in South Korea (PhRMA, 2016).

Exemptions from pharmacoeconomic evaluations and fast track pricing procedures were made available by regulators in May 2015, but originators say few new drugs will meet the narrow qualification criteria. The May 2015 reforms also enable manufacturers to negotiate confidential rebates instead of entering into PVA agreements, but only for drugs that make their global debut in South Korea. More generous launch prices were also unveiled for some new drugs in March 2016, but again, these will be available exclusively to locally developed products (Scrip, 2016). Multinationals, which have labeled these changes as discriminatory, will hope that reforms due to be unveiled later in 2016 will level the playing field. These are expected to award higher launch prices for drugs deemed to offer clinical benefits over existing therapies or treatment regimes.

TURKEY: EXCHANGE RATE ISSUE ADDRESSED, BUT MAJOR PROBLEMS REMAIN

The introduction of a new Pricing Decree in July 2015 will help to ease pressure on originator prices in Turkey. It has not solved exchange rate issues completely, however, while other cost-containment measures will continue to impose severe limits on prices achieved by many original brands.

Maximum prices for new drugs are set using an international referencing mechanism, and caps are adjusted to reflect changing prices in the basket of reference countries. Reimbursement prices must also be established for products seeking access to Turkey’s positive list. This involves the provision by applicants of compulsory discounts, which are set initially at 11%, but which increase sharply, to 41%, after they have been listed for one year (ISPOR, 2012).

Since 2009, the government has also applied a fixed euro/lira exchange rate for pharmaceutical pricing purposes. This was the subject of legal challenges by manufacturers, but remained almost unchanged until 2015. By then, originators estimated that artificially low euro/lira exchange rate calculations had cost them the equivalent of approximately $5bn (PhRMA, 2016).

Finally, on 9 July 2015, the government published a new Pricing Decree which contains an explicit mechanism for calculating and updating the exchange rate that applies to pharmaceutical prices (Mondaq, 2015). This triggered a 4% rise in prices through the remainder of that year, while a new exchange rate was set in January 2016 (Scrip, 2015b).

Referenced launch prices and mandatory discounts on products sold into the institutional market remain in place, and will encourage some manufacturers to continue supplying new drugs through the Turkish Pharmacists Association (TEB; Türk Eczacıları Birlii). Direct purchases by the association of new drugs that have not been added to the national reimbursement list are not subject to either international referencing or mandatory discounts.

The number of products imported by the TEB, and the value of purchases being made through the channel, have both increased dramatically since the beginning of this decade. Purchases are made on a patient-specific basis, and resulting volumes are much lower than those for products on the
reimbursement list. Nevertheless, the TEB route remains attractive for high-value, low-volume products, and is the preferred source of supply for a growing number of patented biologics (Baker & McKenzie, 2015).

Bibliography


REIMBURSEMENT AND FORMULARY ACCESS

In markets where patients are exposed to a substantial proportion of pharmaceutical costs, and where private health insurance coverage is limited, public sector reimbursement listings are a crucial driver of demand for innovative new drugs. Funds available to support such listings are in short supply, however, and financial considerations act as a major barrier to reimbursement in many BRIC/MIST markets (Brazil, Russia, India, China, Mexico, Indonesia, South Korea, and Turkey). Manufacturers may be required to give substantial ground on price in order to achieve listings, and even where innovative new drugs are reimbursed, their use is often limited by the imposition of highly restrictive prescribing controls.

Notwithstanding these limitations, governments are under growing pressure to subsidize the provision of novel drugs, especially where they are indicated for use in the treatment of life-threatening conditions, or where they offer substantial improvements over existing treatments in terms of therapeutic efficacy or safety. Policymakers in most BRIC/MIST countries are already pursuing efforts to reimburse more new drugs, but manufacturers are being asked in effect to subsidize their provision, or to shoulder a proportion of the financial risks associated with their reimbursement.

Where reimbursement prices or other listing terms are deemed overly restrictive, some manufacturers may opt to forego public sector reimbursement, preferring to pursue opportunities in the private sector. These vary enormously between individual markets, and in accordance with the price, indications, and settings in which a drug is administered. As a result, tailored strategies must often be adopted, not just for individual products, but also for the same product in individual markets.

Major reimbursement issues

LIMITED SCOPE OF DRUG SUBSIDIES

South Korea and Turkey aside, access to reimbursed outpatient drugs remains limited in most BRIC/MIST markets. Patients in some countries, including China, must also contribute a percentage of costs associated with inpatient care. Co-payments alone may effectively rule out the treatment of poor patients with expensive hospital drugs where this is the case.

Where outpatient subsidies exist, they are often available under specific schemes designed to provide access to essential medicines for the poorest segments of BRIC/MIST patient populations. These schemes are usually accompanied by explicit formularies that are dominated by well-established drugs available at low prices from multiple manufacturers. Examples include Mexico’s Seguro Popular scheme and Brazil’s Farmácia Popular program, both of which provide access to free or heavily subsidized basic medicines in public health facilities. State governments in India have also established basic drug subsidy programs, which have triggered sharp increases in demand from millions of poor patients for whom treatment with such products was not previously an option.

Providing access to more expensive drugs for the treatment of serious, life-threatening diseases poses a more significant challenge for most BRIC/MIST governments. Several operate well-established catastrophic coverage programs, but financial considerations often limit the scope of formularies
attached to such initiatives. Russia’s seven nosologies program (VZN) covers just seven rare diseases and involves the treatment of fewer than 200,000 patients. Brazil’s specialist pharmaceutical assistance program (CEAF; Componente Especializado da Assistência Farmacêutica) is much broader in scope, but has emerged as a major driver of rising government drug costs – partly because thousands of patients have pursued legal action in order to access innovative medicines, overriding listing decisions or usage restrictions. There are also signs that a similar trend may be emerging in Mexico, where few new drugs have been added to major formularies in recent years.

LENGTHY, NON-TRANSPARENT REIMBURSEMENT PROCEDURES

Where reimbursement lists exist, gaining access can be a lengthy and frustrating process for originators. Review procedures and timelines may exist on paper, but are often either not adhered to or do not provide a clear indication of the factors that determine listing decisions. On average, the reimbursement review process in Turkey still takes the best part of one year, despite commitments by regulators there to deliver more timely decisions.

In China, manufacturers play no direct role in the national reimbursement listing process. Denied the chance to request inclusion on the National Reimbursement Drug List (NRDL), or to interact with reimbursement officials during the review process, they must pursue alternative avenues, working with stakeholders such as patient organizations and the medical profession to build demand for listings.

Pharmacoeconomic reviews and, in one or two countries, full-blown health technology assessments (HTAs) have begun to play a role in reimbursement listing procedures. Committees charged with conducting such reviews often lack the necessary expertise to interpret complex data, however, while cost-effectiveness considerations are often secondary to short-term budget impact analyses where decision-making is concerned. Political factors can also play a role in reimbursement listing decisions, as illustrated by the strong correlation between the outcome of reviews conducted by the National Committee for Health Technology Incorporation (CONITEC: Comissão Nacional de Incorporação de Tecnologias no Sistema Único de Saúde) and the source of requests for formulary inclusion. Two-thirds of all reviews requested by the Brazilian Ministry of Health result in formulary listings, while the figure for external submissions is less than 20% (Interfarma, 2015).

The impact of lengthy review procedures on market access for new drugs is compounded in some BRIC/MIST markets by the failure of regulators to update reimbursement lists on a regular basis. China’s NRDL has been updated only twice since its establishment almost 20 years ago. The most recent update was conducted in 2009, and while a further revision was widely anticipated in 2014, manufacturers are still waiting for its publication.

MULTI-LAYERED ACCESS SYSTEMS

National reimbursement listings do not confer access to the entirety of the institutional market in either China or Mexico. In China, where inclusion on List B of the NRDL is the ultimate goal for most new drugs, provincial formulary managers enjoy a degree of latitude where the replication of national listing decisions is concerned. Specifically, provincial versions of List B may vary by up to 15% from
the NRDL. In the past, it has also taken several months for some provinces to update their formularies in the wake of national Essential Drugs List (EDL) or NRDL updates.

In practice, it is now seven years since the NRDL in China was last revised, and provincial formulary listings have emerged as the key to market access for innovative new drugs. Most originators have focused on the pursuit of listings in the country’s most prosperous provinces and municipalities, but some original brands now feature on the majority of provincial reimbursement schedules.

In some ways, the situation in Mexico has become more problematic. There, the country's two social security institutes, whose affiliates represent the core market for many original brands, conduct their own reimbursement listing reviews. Both face major threats to the stability of their finances, and have pursued increasingly restrictive approaches to the inclusion of innovative new drugs on their respective formularies. This has driven the emergence of growing disparities between the list of hospital drugs contained on Mexico’s national formulary and the range of new medicines available to social security affiliates, prompting some to pursue legal action in a bid to access life-saving treatments.

ACCESSING HOSPITAL FORMULARIES

National or regional formulary listings seldom guarantee that a drug will feature on hospital formularies, which are managed at the individual facility level in most BRIC/MIST markets. Hospital listing committees may meet on a relatively occasional basis, and while physicians may push for the addition of new drugs to existing formularies, financial issues are often a major factor where the listing of costly new drugs is concerned.

Public hospital finances in several BRIC/MIST countries are in poor shape, and where budgets are under severe pressure, funds to support the procurement and use of expensive drugs may be thin on the ground. Even where such products are added to hospital formularies, patterns of use may be erratic, especially where a facility has exhausted its quarterly or annual budget before the end of the relevant financial period. This can prompt the imposition of temporary but drastic cost-containment measures, including a complete stop on the use of costly drugs.

By contrast, financing problems may actually act as a driver of both formulary listings and prescribing activity where drugs represent an income stream for hospitals. This has traditionally been a major factor behind liberal approaches to both formulary listing and prescribing in China’s hospital sector, where most facilities are heavily dependent on profits from drug sales. Efforts are under way to remove the profit motive from hospital drugs, however, and will be stepped up in the future. The reforms have already seen the removal of previously permitted hospital markups on drugs in a growing number of facilities, while plans announced in 2015 will see the imposition of caps on the contribution of drugs to individual hospital income and expenditure totals.

PRICE AS A BARRIER TO REIMBURSEMENT LISTING

Efforts to establish or expand access to subsidized pharmaceutical provision have sharply driven up public sector drug spending in most BRIC/MIST markets, and measures designed to limit the budgetary
implications of reimbursement listings have been stepped up as a result. These have included the establishment of tighter price controls, and the establishment of maximum prices for new drugs is now an integral part of the reimbursement process in some countries.

More recently, regulators have begun to pursue the use of additional tools to limit the budgetary impact of reimbursement listings, including price-volume and/or risk-sharing agreements. While these enable the inclusion of more innovative new drugs on reimbursement schedules, they limit the actual prices that will be achieved by many of the products that are subject to such deals.

To date, manufacturers have generally been willing to give ground on price in return for the volumes that public formulary listings generate. Effective discounting levels in some markets are substantial, however, and where potential volumes are relatively modest, some have chosen to forgo public sector reimbursement. This trend has been most noticeable in Turkey, where the imposition of compulsory discounts and the use of fixed exchange rates to set pharmaceutical prices have had a huge impact on the commercial potential of originator products since the beginning of this decade.

Key national developments

BRAZIL: ECONOMIC TURMOIL BODES ILL FOR PUBLIC FORMULARY LISTINGS

Funds available to bankroll government-subsidized medicines provision are dwindling as the economic climate in Brazil continues to deteriorate. This will have implications not only for new drug reimbursement decisions, but also for volumes generated by products listed on major public formularies.

Having already slashed the federal budget in 2015, the government announced further planned reductions in federal spending in both February and March 2016 (The Rio Times, 2016). The health ministry, which saw its budget cut by 12% in 2015 (BMI, 2015), was among several departments asked to make additional savings. Having contracted by almost 4% in 2015, the Brazilian economy is expected to shrink by a similar amount in 2016, and the federal healthcare budget could be cut further in the coming years (Financial Times, 2016). Existing cuts have already affected funding for some key programs under which patients are able to access free or heavily subsidized medicines.

Drug procurement and prescribing in the public sector is shaped primarily by the National List of Essential Drugs (Relação Nacional de Medicamentos Essenciais). Inpatient drugs are reimbursed in full, but several other formularies provide patients with access to a range of free or low-cost outpatient drugs, antiretrovirals, and some costly innovative drugs for the treatment of catastrophic diseases. Access to public formularies has been administered since 2011 by CONITEC, which reviews the safety, efficacy, pharmacoeconomic, and cost-effectiveness profiles of drugs and other health technologies (CONITEC, 2014).

Between 2011 and July 2015, CONITEC completed 231 drug reviews, of which 215 involved requests for the inclusion of new medicines on public formularies. It approved 80 (37%) of those requests, but refused 60 (28%). A further 41 applications were rejected on the grounds of incomplete documentation, while the remaining 34 were terminated at the request of the applicant (Interfarma,
A closer look at CONITEC activity reveals massive discrepancies in the outcome of reviews depending on the source of requests for formulary inclusion. Where reviews were requested by government agencies (including the health ministry and National Health Surveillance Agency [Agência Nacional de Vigilância Sanitária]), two-thirds resulted in positive appraisals. By contrast, only 19% of external submissions (including those requested by manufacturers) were approved. A further 41% of external submissions were refused outright, 31% were rejected due to deficiencies in supporting documentation, while 9% of applicants requested the termination of reviews. Originators also say most external applications approved by CONITEC have concerned drugs launched several years earlier in other markets (Interfarma, 2015).

Figure 12: Outcomes of completed CONITEC reviews, by source of submission, between 2011 and July 2015

Source: Interfarma, 2015
For innovative new drugs, inclusion on the CEAF formulary, which offers protection against catastrophic costs associated with the treatment of serious diseases, is the ultimate goal. This formulary has been expanded gradually since the beginning of the decade, and now contains approximately 400 presentations of almost 200 drugs (Ministério da Saúde, 2014). Prospects for further near-term expansion look bleak, however, while efforts to limit spending on CEAF-listed drugs will be stepped up as the scheme’s budget is reduced.

Federal funding for the purchase of CEAF drugs by state health authorities in the first quarter of 2014 rose by 5% compared with Q1 2013. An increase of less than 1% was granted in the first quarter of 2015, however, while Q1 CEAF transfers from the federal government to the states in 2016 declined by 5.1% (Ministry of Health, 2016). With inflation having averaged more than 10% in 2015, federal funding for the scheme has fallen by around 15% in real terms (The Wall Street Journal, 2016).

<table>
<thead>
<tr>
<th>Table 10: Outcomes of completed CONITEC reviews, by source of submission, between 2011 and July 2015</th>
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<tbody>
<tr>
<td><strong>Outcome</strong></td>
</tr>
<tr>
<td>Approved for incorporation</td>
</tr>
<tr>
<td>Denied incorporation</td>
</tr>
<tr>
<td>Application rejected (incomplete)</td>
</tr>
<tr>
<td>Application terminated on request</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

Source: Interfarma, 2015
With funding for the provision of new-generation hepatitis C drugs expected to impose additional pressure on federal budgets in 2016, funds to support the subsidized provision of other medicines will remain in short supply. This will limit near-term additions to the CEAF formulary, and could drive the imposition of additional constraints on the use of products already on the list. In turn, this could trigger a further rise in the number of lawsuits being filed by patients seeking access to innovative new drugs. Unique to Brazil, this trend has already emerged as a significant contributor to public sector drug spending, with the majority of cases having been settled in favor of plaintiffs pursuing their constitutional right to healthcare (Biehl et al., 2012).

**ECONOMIC WOES WILL ALSO AFFECT OPPORTUNITIES IN THE PRIVATE SECTOR**

About a quarter of the Brazilian population has access to a degree of private health cover, but affiliate numbers in the sector, which were rising steadily until 2014, have fallen back in the wake of the economic downturn. The private plan beneficiary population peaked at 50.4 million in December 2014, but fell by 1 million (2%) in 2015, and has declined further since then (ANS, 2016). Latest available figures put coverage at 48.8 million in March 2016, some 1.6 million (3.2%) below the recent peak. A further significant decline is anticipated through the remainder of 2016 as the economy continues to contract.

Prevailing conditions will drive the introduction of stronger payer cost-containment measures, including efforts to limit drug spending. As in the public sector, the provision of outpatient drug benefits by private plan providers is limited, and payers have been reluctant to comply with new coverage requirements enforced by the sector's regulator (the National Regulatory Agency for Private Health Insurance and Plans [ANS; Agência Nacional de Saúde Suplementar]). This has seen private plans required to fund the provision of more than 30 oral cancer drugs prescribed on an outpatient basis since the beginning of 2014 (Massard da Fonseca et al., 2016).
RUSSIA: ALL QUIET ON THE REIMBURSEMENT FRONT AS BUDGETS ARE SLASHED AGAIN

Prospects for the establishment of a comprehensive outpatient drug reimbursement scheme in Russia have continued to fade in the face of deteriorating economic conditions. Falling oil prices have forced the government to slash its spending plans in each of the past two years. In January 2016, ministries were ordered to draw up plans for cuts totaling more than $9bn, with state investment programs – which include healthcare – earmarked as the main targets for reduced spending (RT, 2016).

Plans for the phased introduction of a national reimbursement scheme were drawn up in more agreeable economic times. These envisaged that the scheme would be piloted in a number of regions during 2015 and 2016, and that the system would be rolled out nationally in the period from 2017 to 2020 (IMS Health, 2015a). Little has been heard of the initiative since the economy began to falter, however, and the creation of a functioning scheme available to patients throughout the country remains a distant prospect.

In the meantime, the vast majority of Russian patients will continue to foot the bill for outpatient drugs, limiting prospects for the uptake of innovative new medicines. A proportion will not even receive full reimbursement of inpatient drug expenses.

In a country with a population of some 143 million, an estimated 32.8 million individuals (less than a quarter of the total) are currently eligible for full reimbursement of their outpatient drug costs (Popovich and Potapchik, 2015). Of these, the vast majority access subsidized medicines through programs financed by regional authorities, with just 5 million benefiting from federally funded reimbursement initiatives.

Known as the DLO, Russia's current reimbursement program consists of two strands: the ONLS scheme, which provides full coverage of outpatient drug costs for specific groups such as war veterans and their families, and the disabled; and the VZN, which provides coverage for patients with specific diseases such as hemophilia, multiple sclerosis, Gaucher's disease, and cystic fibrosis, as well as for organ/tissue transplants. Separately, federal coverage is available for patients with HIV, tuberculosis, and hepatitis, while regional governments are required in theory to provide coverage for patients with cancer and diabetes, although access to regionally funded drugs varies widely in practice.

Almost 15 million people were covered by the DLO when it was established around 10 years ago. Beneficiaries were offered cash benefits in lieu of reimbursement coverage, however, and many have chosen that option. Coverage has dwindled progressively as a result, and now stands at less than 5 million, most of whom suffer from chronic health problems.

VZN UPDATE

The VZN covers less than 200,000 patients, and while plans to broaden coverage by adding more orphan diseases to the scheme have been discussed, there is little prospect of expansion in the prevailing economic climate (Yampolsky, 2015). In the meantime, more drugs have been listed for the treatment of the seven conditions covered by the scheme.
Johnson & Johnson's Velcade (bortezomib) was previously the only multiple myeloma drug reimbursed under the VZN scheme, but Celgene's Revlimid (lenalidomide) was added to the list when it was updated in March 2015. The 2015 update also saw Shire's Vpriv (velaglucerase alfa) listed for the treatment of Gaucher's disease, offering an alternative to Genzyme's Cerezyme (imiglucerase) (Yampolsky, 2015).
### Table 12: Additions to the VZN reimbursement schedule, 2015

<table>
<thead>
<tr>
<th>Established list</th>
<th>Additions</th>
</tr>
</thead>
<tbody>
<tr>
<td>bortezomib (Velcade)</td>
<td>Anti-inhibitor coagulant complex</td>
</tr>
<tr>
<td>Coagulation factor IX</td>
<td>Coagulation factor VIII + von Willebrand factor</td>
</tr>
<tr>
<td>Coagulation factor VIII</td>
<td>Lenalidomide (Revlimid)</td>
</tr>
<tr>
<td>cyclosporine</td>
<td>moroctocog alfa (ReFacto)</td>
</tr>
<tr>
<td>dornase alfa (Pulmozyme)</td>
<td>velaglucerase alfa (Vpriv)</td>
</tr>
<tr>
<td>eptacog alfa (NovoSeven)</td>
<td></td>
</tr>
<tr>
<td>fludarabine</td>
<td></td>
</tr>
<tr>
<td>glatiramer acetate</td>
<td></td>
</tr>
<tr>
<td>imatinib (Glivec)</td>
<td></td>
</tr>
<tr>
<td>imiglucerase (Cerezyme)</td>
<td></td>
</tr>
<tr>
<td>interferon beta-1a</td>
<td></td>
</tr>
<tr>
<td>interferon beta-1b</td>
<td></td>
</tr>
<tr>
<td>mycophenolate mofetil</td>
<td></td>
</tr>
<tr>
<td>mycophenolic acid</td>
<td></td>
</tr>
<tr>
<td>octocog alfa (NovoSeven)</td>
<td></td>
</tr>
<tr>
<td>rituximab (Rituxan)</td>
<td></td>
</tr>
<tr>
<td>somatropin (Nutropin)</td>
<td></td>
</tr>
<tr>
<td>tacrolimus</td>
<td></td>
</tr>
</tbody>
</table>

Source: Yampolsky, 2015

**INDIA: NEW “CATASTROPHIC COVERAGE” SCHEME UNVEILED, BUT NO NEWS ON NHAM**
In its budget for the year to March 2017, the Indian government unveiled a new health protection scheme offering up to $1,500 per family to cover hospitalization expenses. Critics say coverage offered by the new scheme will not make a major difference, however, given the scale of costs associated with most catastrophic disease cases. Nor, despite an overall increase of 13% in government health expenditure, did the latest budget offer any indication that the government intends to implement major healthcare reforms in the near future (The Times of India, 2016).

In his 2014 election manifesto, Prime Minister Narendra Modi pledged to create a National Health Assurance Mission (NHAM) offering universal access to basic healthcare provision. A national health policy (NHP) document drafted in that year identified universal access to free essential medicines as a key goal (MoHFW, 2014). Little has been heard of the NHAM since then, however, while efforts to establish a network of government-run low-cost generic dispensing outlets have made little progress.

In the absence of a stronger lead by the national government, state administrations have emerged as the main providers of subsidized medicines to the poor. These have had a significant impact, but involve the provision of low-cost generics, and do not address the needs of many patients with serious, life-threatening conditions who could be treated with more expensive medicines.

The NHP draft released in December 2014 quoted WHO estimates that catastrophic healthcare costs tip over 60 million people in India into poverty every year (MoHFW, 2014). With drugs reckoned to account for around two-thirds of all out-of-pocket spending on healthcare, medicine costs are clearly a major contributor to that pernicious trend.

The NHP called for a rise in government health expenditure towards 2.5% of gross domestic product (GDP) by 2020 (MoHFW, 2014). The figure currently stands at little more than 1%, however, and appears unlikely to come anywhere near that target within the stipulated timeframe.

With most private health plans providing lump sum payments rather than the reimbursement of specific treatments, reimbursement for innovative medicines remains virtually non-existent in India. In its absence, access to new drugs is a huge problem, with manufacturer-led initiatives offering some of the few partial solutions on offer. Others are being provided by companies offering medical loans, some of which have established access partnerships with manufacturers. This approach is still in its infancy, however, and will not represent a viable option for the country's poorest patients. Arogya Finance, which is among the early entrants in the sector, offers loans worth up to $3,000 covering up to 75% of total medical bills, but conducts credit checks on patients before approving payments (Arogya Finance, 2016).

CHINA: NRDL UPDATE IN THE OFFING?

Speculation that China may soon update its NRDL has increased in the wake of announcements that national prices have been negotiated for a handful of innovative new drugs, including two cancer medicines and a hepatitis B treatment. The list was last updated in 2009, and originators have long been pressing for an update. Frustrated by continued delays, industry representatives called for the establishment of rolling updates to the list when they met with regulators in March 2016 (Scrip,
In the absence of more frequent updates to the NRDL, provincial reimbursement listings have emerged as the main target for originators pursuing access to the Chinese market for new drugs. Provincial lists vary considerably, however, and coupled with differences in coverage provided by the country's three main social health insurance schemes, this has made for an increasingly complex reimbursement environment.

The reimbursement listing process is not only complex, but also extremely time-consuming, while negotiating access to provincial reimbursement lists invariably involves the provision of substantially discounted prices for innovative drugs. Originators have called for the implementation of more frequent, regular updates of both national and provincial lists, and for the establishment of more transparent, predictable reimbursement review procedures (PhRMA, 2016).

Access to subsidized medicines for affiliates of China's co-operative rural health insurance scheme is limited to products on the country's EDL, while beneficiaries of the two urban health insurance programs have access to products on the NRDL. The latter comprises two lists: List A, which contains essential drugs that must be reimbursed in full by all provinces; and List B, which contains more complex products for which provinces have some leeway where both listings and levels of reimbursement are concerned. The 2009 version of the NRDL contains over 2,000 products, of which more than 1,100 are modern (“Western”) pharmaceuticals (Gross, 2010).

Provincial and local authorities have considerable scope for variation in their interpretation of national lists, while there are also significant discrepancies in the levels of reimbursement available to patients in individual provinces. Coverage is often limited to inpatient treatment, although some more prosperous provinces offer outpatient drug benefits (China Business Review, 2011).

The widespread absence of outpatient reimbursement and the need to foot a proportion of the bill for the most expensive inpatient medicines still limits access to innovative drugs for many patients. Healthcare reform plans envisage a gradual increase in both the breadth and extent of reimbursement coverage, however. A significant development in this regard was the establishment in 2012 of a new Critical Illness Insurance Program (CIIP). This aims to reimburse at least 50% of all costs related to the treatment of 20 catastrophic diseases, including conditions such as gastric cancer and childhood leukemia (Deloitte, 2014). Like so many other initiatives, however, implementation of the CIIP and the degree of coverage being provided vary widely between provinces.

RICHER PROVINCES LEAD THE WAY

Provincial and local authorities have continued to update their respective reimbursement lists in the absence of an NRDL update. This has resulted in a steady stream of provincial formulary listings, some of which are now considerably more comprehensive than the NRDL.

There is a strong correlation between provincial listing activity and the respective prosperity of individual provinces or municipalities, and most originators have focused their efforts on the pursuit
of listings in these regions. Provincial lists are most expansive in areas such as Jiangsu and Guangdong, and in the country's major municipalities (Beijing, Tianjin, and Shanghai). These are key targets for originators seeking inclusion on Provincial Reimbursement Drug Lists (Deloitte, 2014).

Herceptin (trastuzumab; Roche/Chugai), Tarceva (erlotinib; Genentech/Roche/Chugai/Astellas), MabThera (rituximab; Roche), and Ezetrol (ezetimibe; Merck & Co) are among high-profile multinational brands that are an established presence on some provincial/municipal reimbursement lists. As well as generating more substantial volumes, provincial listings are seen by manufacturers as a means of building the critical mass required to tip the scales in favor of an NRDL listing when the national reimbursement formulary is eventually updated (Deloitte, 2014).

MEXICO: LENGTHY, MULTI-LAYERED LISTING PROCESS FRUSTRATES ORIGINATORS

Several new oncology drugs and the first representatives from the gliflozin diabetes treatment class were among new products added to Mexico’s national formulary in 2015. None of these products is being reimbursed by the Social Security Institute (IMSS; Instituto Mexicano del Seguro Social) in 2016, however, underlining the challenges faced by originators attempting to access Mexico’s silo-like healthcare system.

The IMSS is one of three major institutions involved in the funding and provision of public healthcare. An equivalent institute, the Institute for Social Security and Services for State Workers (ISSSTE; Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado), administers provision for civil servants and their dependents, while the Ministry of Health (MoH) funds and manages a People’s Health Insurance scheme (Seguro Popular), which caters for over 50 million people who do not possess employment-related health insurance (World Bank, 2015). Each of these three agencies operates its own health infrastructure, and each uses its own formularies to determine the availability of medicines to its affiliates.

Manufacturers seeking reimbursement of a new drug must submit applications to the General Health Council (CSG; Consejo de Salubridad General). Applications are scrutinized by a multi-agency commission on which the IMSS, ISSSTE, and MoH are all represented. The process, which involves a review of pharmacoeconomic data, results in the listing or exclusion of a drug on one or both of two national formularies: the Cuadro Básico, which lists drugs for use in the primary care setting, and the Catálogo de Insumos, which lists products for use in secondary and tertiary care (CSG, 2015).

National listings do not guarantee access to IMSS, ISSSTE, or MoH formularies, however, since each of the three agencies operates its own two-strand formulary. Notwithstanding their representation on the national listing commission, both social security institutes conduct their own separate listing reviews. Each is wrestling with huge pension liabilities that have triggered a major cost-containment drive, resulting in a marked reluctance to include costly new drugs on their respective formularies. Having added 24 products to its formulary in 2011, the IMSS included only 12 in 2012 and just four in 2013. The ISSSTE, which listed more than 30 new drugs on its formulary in 2011, added two in 2012 and none in 2013 (IMS Health, 2014).
More than half a dozen biologics listed on the Catálogo de Insumos for the treatment of cancer do not feature on the IMSS’s 2016 formulary (CSG, 2015; IMSS, 2016). The list of omissions includes some products, such as erlotinib, gefitinib, and lapatinib, which were added to the national formulary more than five years ago. Nor, where the treatment of diabetes is concerned, does the IMSS reimburse treatment with any member of the gliptin class, despite the appearance of three gliptins on the Catálogo de Insumos.

<table>
<thead>
<tr>
<th>Oncology</th>
<th>Diabetes mellitus</th>
<th>Rheumatology</th>
</tr>
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<tbody>
<tr>
<td>axitinib</td>
<td>dapagliflozin</td>
<td>belimumab</td>
</tr>
<tr>
<td>crizotinib</td>
<td>denosumab</td>
<td>golimumab</td>
</tr>
<tr>
<td>denosumab</td>
<td>empagliflozin</td>
<td></td>
</tr>
<tr>
<td>erlotinib</td>
<td>linagliptin</td>
<td></td>
</tr>
<tr>
<td>gefitinib</td>
<td>saxagliptin</td>
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<tr>
<td>ipilimumab</td>
<td>vildagliptin</td>
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<tr>
<td>lapatinib</td>
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<tr>
<td>pertuzumab</td>
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All of the above drugs had been listed on the Catálogo de Insumos by 2015.

Originators say that, over the past three years, fewer than 10% of innovative medicines seeking access to reimbursement have been listed on key formularies managed by the IMSS, ISSSTE, and MoH. They calculate that, on average, reimbursement delays add more than two years to the time taken for new drugs to gain market access in Mexico. Some innovative medicines that have been reimbursed widely in other countries have been denied listings outright in Mexico, with regulators or formulary managers raising questions regarding their efficacy or safety (PhRMA, 2016). Originators will continue to lobby for improvements in the efficiency and transparency of the reimbursement process.

INDONESIA: NCDS A KEY TARGET FOR NEW NATIONAL FORMULARY

Access to subsidized medicines under Indonesia’s new national health insurance scheme (JKN; Jaminan Kesehatan Nasional) is governed by a new national formulary (Fornas), which was drawn up
by the MoH in 2013. Based on the country's pre-existing essential medicines list, but including a number of significant additions, it initially contained 514 active ingredients from 29 therapeutic classes. The formulary was updated in 2015, and now contains 573 active ingredients (Depkes, 2015).

The Fornas is considerably more comprehensive than either the current WHO Essential Medicines List (EML) or those in several other BRIC/MIST markets, including China, Brazil, and India. Coverage of major non-communicable diseases (NCDs) such as cancer, cardiovascular disease, and diabetes is particularly broad by emerging market standards. The Fornas contains 42 cardiovascular drugs, 44 oncology medicines, and 15 diabetes products, compared with current WHO EML totals of 23, 30, and five, respectively. Notable listings include monoclonal antibody-based cancer drugs (bevacizumab, erlotinib, gefitinib, imatinib, nilotinib, and rituximab) and the new-generation diabetes treatment pioglitazone (IMS Health, 2015b).

The JKN has run up sizable deficits since its introduction at the beginning of 2014, prompting a number of early interventions designed to stabilize its finances. These have included adjustments to some provider payments and a hike in premiums paid by affiliates (EIU, 2015). Efforts to limit drug spending have also been stepped up, and the scale of early financial problems could prompt the pursuit of a more restrictive approach to reimbursement.

SOUTH KOREA: RISK SHARING OFFERS BROADER NHI ACCESS, BUT AT A PRICE

Introduced at the beginning of 2014, risk-sharing agreements (RSAs) could improve access to South Korea's national health insurance (NHI) reimbursement schedule for innovative new drugs. Only a handful of agreements have been struck to date, however, and some manufacturers may be reluctant to enter into such deals, given their potential impact on returns that will be limited further by low launch prices.

The establishment of an RSA mechanism is part of a broader drive to improve NHI coverage in four key areas: cancer, cerebrovascular disease, cardiovascular disease, and rare incurable diseases. Government figures show that patients with cancer, cerebrovascular disease, and cardiovascular disease were exposed to more than a quarter of costs associated with their treatment in 2012, while those with rare incurable diseases contributed approximately 15% (NHIS, 2014). Policymakers are aiming to achieve 100% coverage of curative treatments by 2016.

To date, it has been especially difficult for oncology drugs and products for the treatment of rare diseases to gain access to reimbursement. Between 2007 and July 2014, around 69% of new drugs seeking reimbursement were listed on the NHI schedule, but success rates for rare disease treatments (64%) and cancer medicines (61%) were noticeably lower (ISPOR, 2014). The time taken for cancer drugs to achieve a reimbursement listing was also much higher than average (over 41 months, compared with an overall average of less than 25 months).
A significant proportion of unsuccessful listing requests were the result of negative HTAs undertaken by the Health Insurance Review & Assessment Service. RSAs offer manufacturers the chance to sidestep that barrier, providing that they are willing to fund a proportion of costs associated with the use of a new drug. Early RSAs have featured coverage with evidence development agreements, money-back guarantees for usage in unresponsive patients, and refund contracts (WHOCC, 2014).

Among the first agreements struck were RSAs for Sanofi’s pediatric leukemia drug Evoltra (clofarabine), Merck & Co’s colon cancer drug Erbitux (cetuximab), and Celgene’s multiple myeloma treatment Revlimid (lenalidomide). While exact RSA terms are confidential, agreements on Erbitux and Revlimid will see manufacturers refund costs associated with the treatment of non-responsive patients (WHOCC, 2014).

Having attracted only a handful of early applicants, regulators may consider changes to the RSA scheme in a bid to elicit more interest, and may relax some current qualification criteria. Coupled with the potential introduction of higher prices for truly innovative new drugs, this could trigger an increase in manufacturer interest.

Separately, regulators have announced plans to pilot a scheme under which regulatory review and HTA assessment procedures will be combined for innovative new drugs, resulting in the delivery of a final decision on both marketing approval and reimbursement status by the Ministry of Food and Drug Safety. With regulatory experts in both areas communicating at an early stage, the aim is to reduce the frequency with which subsequent demands for additional data are made, expediting HTA assessment procedures (ISPOR, 2016).

**TURKEY: SGK STRIKES DEAL ON HEPATITIS C DRUGS**
In July 2016, the Turkish Social Security Institution (SGK; Sosyal Güvenlik Kurumu) announced a deal reached with Gilead and AbbVie under which patients will gain access for the first time to reimbursed new-generation hepatitis C drugs. Essentially a price-volume agreement, the deal involves Gilead's Sovaldi (sofosbuvir) and Harvoni (ledipasvir/sofosbuvir), as well as AbbVie's ombitasvir/paritaprevir/ritonavir combination product, sold in Turkey as Viekirax. Both companies agreed to supply their products at prices significantly below list price levels in return for purchasing guarantees issued by the SGK (Scrip, 2016b).

This deal could set a precedent, paving the way for similar agreements covering other innovative new drugs, including oncology products. As such, it represents a welcome development for originators, which have seen the reimbursement climate in Turkey deteriorate significantly in the face of a concerted pharmaceutical cost-containment drive.

Turkey’s health transformation program has seen the SGK emerge as the country’s major pharmaceutical payer, reimbursing almost 75% of all prescription drug costs (Gürsoy, 2016). Widespread access to free or heavily subsidized medicines has sharply driven up demand, however, prompting the imposition of tougher pricing and reimbursement rules that have seen public sector drug spending fall below pre-reform levels when expressed as a proportion of GDP.

Current pricing and reimbursement rules include the provision of mandatory discounts on products admitted to the national positive list. For most original brands, these are levied at 41% (Gürsoy, 2016). Some manufacturers have reportedly offered even larger discounts, but others have shunned...
the positive list, importing some high-cost drugs through the national pharmacists' association on an ad hoc basis (Scrip, 2016c).

Since July 2015, reimbursed cancer drugs have no longer been dispensed outside hospitals, while some new oncology products have either been denied access to reimbursement or have been the subject of more restrictive listing conditions (Hurriyet Daily News, 2015). Further efforts to rein in reimbursement spending were unveiled in February 2016, including the creation of a new commission charged with drafting new reimbursement models designed to encourage the local manufacture of innovative drugs. Article 46 of the government's latest “immediate action plan,” published in December 2015, calls not just for the provision of preferential reimbursement arrangements for locally manufactured drugs, but also for the delisting of imported products from the national reimbursement list where appropriate (Scrip, 2016d).

A new law implemented in 2014 allowed for the negotiation of RSAs with applicants seeking the inclusion of costly new drugs on the positive list, but that approach may now be overtaken by price-volume agreements if the SGK is willing to pursue such negotiations on a broader basis.

Originators remain unhappy with reimbursement procedures, which they say are both lengthy and lacking in transparency. Some improvement in average reimbursement review times has been witnessed since the beginning of this decade, but manufacturer surveys show that the average wait for reimbursement listing decisions following receipt of a marketing authorization is still 235 days (PhRMA, 2016).

**FORMER NOVARTIS CONSULTANCY AT THE CENTER OF BRIBERY ALLEGATIONS**

In March 2016, it emerged that a consultancy firm employed by Novartis to act on its behalf in negotiations with Turkish government officials was at the center of an alleged bribery scandal. The allegations are said to have been contained in a leaked email sent by an anonymous whistleblower to high-ranking Novartis executives (Reuters, 2016).

The email alleged that the Alp Aydin Consultancy was paid $290,000 plus costs by Novartis, and was able to obtain hospital formulary listings for Novartis drugs used in the treatment of multiple sclerosis, chronic lung disease, and juvenile arthritis. Novartis reportedly ended its association with the consultancy after the authorities launched an investigation into the matter (Reuters, 2016).

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PUBLIC SECTOR PROCUREMENT

Institutional purchases are a major source of demand for medicines in most BRIC/MIST markets (Brazil, Russia, India, China, Mexico, Indonesia, South Korea, and Turkey). In some, their role as a driver of patented drug sales is even more important, reflecting low levels of patient purchasing power and limited levels of access to private health cover. Government drug budgets are also limited, however, and have come under growing pressure as a result of rising costs, coverage expansion, and, in countries such as Brazil and Russia, a sharp deterioration in the state of public sector finances. This has seen policymakers step up efforts to curb government drug spending, and procurement costs are a common target.

Even where government agencies play a limited role in drug procurement, policies are designed to encourage purchasing at low prices. Thus, while individual hospitals tender for the supply of inpatient drugs in South Korea, they have been encouraged to lever the best possible prices on medicines by regulations that enable providers to retain a proportion of the difference between actual purchase prices and national health insurance (NHI) reimbursement prices. Since discount-based price cuts are a feature of the South Korean pricing and reimbursement landscape, this erodes reimbursement prices over time. Hospital-level tenders also dominate inpatient drug purchasing in Turkey, which, like South Korea, has established a universal health insurance system. Drugs funded by the country’s Social Security Institution (SGK; Sosyal Güvenlik Kurumu) are subject to mandatory discounts, however, with these levied at the highest rates (41%) on most original brands.

Procurement strategies as a cost-containment tool

BULK PURCHASING IS BEING USED TO LEVER DOWN PUBLIC SECTOR PURCHASE PRICES

Logistical, financial, and administrative shortcomings have acted as historical barriers to the consolidation of public sector procurement in most BRIC/MIST markets, while corrupt practices have undermined the impact of bulk purchasing initiatives in some. Tighter regulation of the sector and the development of more robust administrative capabilities have enabled public agencies to begin leveraging their combined purchasing power more effectively in several countries, however. By guaranteeing substantial volumes to suppliers, these bodies can extract significant discounts on drugs purchased for use in public hospitals and health centers.

New national procurement agencies have been established recently in both Indonesia and India. Both are focused on the procurement of low-cost generics, however, and while some originators may be prepared to offer low prices for certain brands in order to access Indonesia’s new NHI scheme, tenders issued by India’s Central Medical Services Society (CMSS) will be of little interest to multinationals.

More significant developments have been witnessed in Mexico, where the Social Security Institute (IMSS; Instituto Mexicano del Seguro Social) is administering tenders on behalf of a growing number of public sector procurement agencies. Some previously issued their own tenders for supply at volumes far below those purchased by the IMSS. In a sector marked by previously limited levels of price transparency, procurement prices varied widely, and bulk purchasing for these agencies by the institute has levered significant savings – not just on multi-source drugs, but also on a number of
original brands.

NEW TENDER MODELS AND INFORMATION SHARING ARE BOTH ERODING AVERAGE PURCHASE PRICES

The adoption of more aggressive tendering models has also been used to drive down public sector procurement prices. This has seen a growing number of major purchasing agencies switch from single, sealed-bid procedures to reverse-auction tenders conducted using online platforms. These see the most competitive bidders invited to submit second offers, invariably securing prices below those tendered in the first round.

In an effort to preserve the security of public sector supply, most tenders are split. The largest share of a contract is invariably awarded to the lowest bidder, but one or more other suppliers will also be engaged. Where regulators have begun to impose tighter quality standards on bidders, confidence in the ability of individual companies to meet their supply obligations is rising. This has prompted purchasing agencies to begin offering a larger proportion of contracts to the lowest bidder. Again, this encourages the submission of more competitive bids, since securing the bulk of a contract guarantees significantly larger volumes.

Information on the outcome of tenders is also being disseminated more widely, often through online platforms that can be accessed by other public sector purchasing agencies. Armed with information on prices offered by suppliers in other segments of the market, these agencies are in a stronger position to ensure that they obtain a fair price for the products in question. Such information is particularly valuable where the purchase of patented products and other single-source drugs is concerned.

IMPORT SUBSTITUTION POLICIES FAVOR THE PURCHASE OF LOCALLY MANUFACTURED PRODUCTS

Originator products are purchased and prescribed at modest volumes in the institutional sector of most BRIC/MIST markets. They impose a disproportionate burden on public sector drug budgets, however, and costs associated with the purchase of imported medicines have been driven up sharply in the wake of recent currency fluctuations. This has prompted some governments to step up import substitution policies, encouraging increases in both the volume and scope of local manufacturing activity.

Recent developments in Russia have been most notable in this regard, but policies that hand a significant advantage to local manufacturers – especially where access to institutional market segments is concerned – are also a feature of several other BRIC/MIST countries. Procurement rules in both Russia and Brazil allow local manufacturers to compete for (and win) public tenders at higher prices than their overseas counterparts. Rules enabling foreign companies to qualify as local manufacturers are also being tightened in Russia, where the conducting of local primary or secondary packaging will no longer be sufficient to confer local manufacturer status from the beginning of 2017 (Scrip, 2015). Elsewhere, policies designed to encourage more companies to switch from import-based supply strategies to local manufacture are being pursued in Brazil, Turkey, and Indonesia.
In January 2016, the Turkish government announced plans to offer a seven-year procurement contract to a foreign company willing to invest in the construction of a hepatitis A vaccine manufacturing facility in the country (PhRMA, 2016). In Brazil, meanwhile, procurement contracts are being offered to foreign companies willing to enter into technology transfer agreements that will enable state-owned facilities to begin manufacturing a range of high-cost drugs (Outsourcing Pharma, 2014).

The willingness of originators to invest more heavily in BRIC/MIST manufacturing capabilities will depend on a range of factors, including regional or global supply considerations as well as the size of local market opportunities. The intellectual property protection climate in individual BRIC/MIST countries and the willingness of regulators to address other outstanding market access issues such as local trial requirements, registration delays, and pricing and reimbursement rules will also play a role.

**Key national developments**

**BRAZIL: DISCOUNTS CONTINUE TO LIMIT INSTITUTIONAL PURCHASE PRICES**

Already capped by the application of an international referencing mechanism, the prices of new drugs sold into Brazil's institutional market are limited further by the imposition of compulsory discounts. In 2016, these will knock almost 19% off the manufacturer price of original brands purchased by public health agencies (ANVISA, 2016), with centralized purchasing and discounts levered by hospitals driving the purchase price of some drugs down even further.

Known as price adjustment coefficients, compulsory discounts are calculated by benchmarking per capita gross domestic product figures in Brazil against those in a basket of other countries. They are applied to manufacturer prices to arrive at a maximum government sales price (Preço Máximo de Venda ao Governo). In the early part of this decade, the mechanism was cutting public sector purchase prices by around 22%. The figure has fallen since then, and stands at just under 18.8% in 2016 (ANVISA, 2016), but is likely to rise again if the Brazilian economy continues to contract.

Reverse auction tendering for multi-source drugs means few originators pursue public sector supply contracts once their brands are exposed to generic competition. Brazil's catastrophic drugs fund (Componente Especializado da Assistência Farmacêutica) generates significant demand for some patented products, however, while volumes in the sector have been boosted considerably by patient lawsuits seeking access to innovative medicines. Significantly, drugs funded by the government in line with judicial requirements are also subject to compulsory discounts.

**MOST MULTINATIONAL PDP APPLICATIONS ARE REJECTED**

Discounted prices have also been negotiated in return for commitments to purchase drugs that are the subject of technology transfer agreements designed to encourage local production of drugs that exert significant cost burdens on the Brazilian public health system (SUS; Sistema Único de Saúde). Known as productive development partnerships (PDPs; Parceria para o Desenvolvimento Produtivo), these generally involve the transfer of technology from private companies to state-owned manufacturing laboratories which, the government hopes, will eventually produce a growing range of biologics, cutting SUS expenditure on these products. In return for discounts offered by private
companies over the duration of PDP agreements, the government guarantees to purchase the products involved for use in public programs.

While the PDP initiative was established almost a decade ago, few agreements have so far come to fruition. The prospect of guaranteed volume sales in the institutional market has become increasingly attractive, however, and more than half a dozen multinationals submitted PDP applications during the first quarter of 2015. Most did so in partnership with local manufacturers, but competing applications submitted exclusively by domestic companies were awarded most new PDP contracts when these were announced in October 2015. Among the submissions rejected by regulators were technology transfer programs proposed by AbbVie for adalimumab, Janssen-Cilag for darunavir, Sanofi for docetaxel, Merck & Co for raltegravir, and GlaxoSmithKline for a controlled-release salbutamol product (MoH, 2016).

RUSSIA: GOVERNMENT STEPS UP IMPORT SUBSTITUTION DRIVE

With its economy contracting sharply and the ruble plunging in value against the dollar, the Russian government ramped up import substitution policies during 2015 in a bid to limit costs associated with the purchase of foreign drugs. The new measures, which will exacerbate existing problems for originators pursuing access to the Russian market, were branded as discriminatory by foreign manufacturers, which said some new rules may be in breach of the country’s World Trade Organization commitments (PhRMA, 2016).

Existing public procurement rules confer a 15% price advantage to local manufacturers tendering for the supply of multi-source drugs, and local producers were previously awarded tender contracts where their offer matched that of a foreign supplier. Now, however, foreign suppliers may be frozen out of tenders completely if two or more manufacturers based in the Eurasian Economic Union submit bids. Outlined in a November 2015 Resolution (No 1289), the new rules apply to tenders for any product on the Essential Drugs List. Until the end of 2016, local packaging or repackaging activity will be sufficient for foreign companies to avoid these restrictions. From the beginning of 2017, however, they will be required to conduct full-scale local production in order to maintain or obtain local manufacturer status (Scrip, 2015).

Foreign companies, including a growing number of originators, have stepped up levels of investment in Russia, largely in a bid to qualify as local manufacturers. Several major insulin producers, including Novo Nordisk and Sanofi, have established Russian manufacturing plants, but the market is still dominated by imports, which account for almost 90% of all insulin sales. These revenues could now be under serious threat following a call by President Putin for the Ministry of Health to develop policy proposals on the establishment of centralized state insulin procurement from a single, local supplier. The most likely beneficiary of such a move would be the state corporation, Rostec, which has announced plans to invest some $350m in the development of a new, full-cycle insulin production plant by its Bioran subsidiary (The Pharma Letter, 2015).

INDIA: CMSS ISSUES FIRST NATIONAL DRUG TENDERS

Centralized procurement agencies have been established by state governments attempting to squeeze
the most out of limited budgets for the purchase of drugs dispensed free to poor patients under state-level basic health insurance schemes in India (WHO, 2013). The success of these initiatives prompted India’s national government to set up its own centralized purchasing agency, the Central Medical Services Society (CMSS), in 2012 (MoHFW, 2014).

The CMSS issued its first tenders two years later, and while activity has been dominated by the purchase of other medical inputs, it has since invited several bids for the supply of drugs, including tuberculosis products (RFP Alert Services, 2016). Like state-level agencies, however, CMSS purchases are dominated by low-cost generics, and are of little interest to originators.

CHINA: PROCUREMENT OVERHAUL TO HEAP MORE PRESSURE ON DRUG PRICES

China’s complex public sector drug purchasing environment is set for a major overhaul, which, while possibly encouraging more harmonized approaches across the country, will also impose additional downward pressure on prices. With sales through public hospitals dominating the Chinese market, this will have major implications for all manufacturers, including originators.

Hospital drugs are procured largely through tenders issued at provincial or city level, but the size of contracts, their duration and timing, and the nature of bidding procedures all vary widely. Policymakers have now called for the nationwide implementation of new approaches to procurement, partly in a bid to regulate purchasing more effectively, but also to help drive down public sector drug spending. The new approach was outlined in guidelines issued by the government in February 2015, and was fleshed out in a second document issued by the National Health and Family Planning Commission (NHFPC) later in the year (China Healthcare Outlook, 2015).

The changes will have particular implications for original brands exposed to generic competition, with no distinction being made between these two categories in tender contracts issued under the new system. Patented brands and other single-source drugs will be purchased through negotiations with suppliers, but the outcome of these negotiations will be made available publicly through a national database. By enabling all purchasing agencies to gauge the outcome of such negotiations, this increase in levels of price transparency is expected to drive down average procurement prices. Where procurement is managed at the city level, supply agreements may not be struck at levels in excess of relevant provincial bid prices. In addition, if city-level procurement agencies strike supply deals at levels below provincial prices, the latter must automatically be reduced (CNGJZI, 2015).

In a bid to guarantee the quality of drugs procured for use in public hospitals, all tenders must be based on a double envelope system, with bidders required to furnish technical/quality assurance details as well as a bid price. Technical documentation will be scrutinized closely where bid prices differ significantly from those submitted by other competitors (China Healthcare Outlook, 2015).

While bid prices accepted by provincial or city purchasing agencies supposedly apply across the entirety of their respective jurisdictions, secondary price negotiations – though strictly illegal – have been a common feature of the institutional market to date. Originators in particular will be keen to ensure that, given the additional pressure imposed on prices by increases in transparency, bid prices
hold more firmly in future. This will be particularly important for companies that have negotiated the first national-level prices for patented drugs, which were announced during the first half of 2016. National regulators have given assurances that these prices will not be subject to renegotiation at provincial, local, or hospital level (NHFPC, 2016), but it remains to be seen whether manufacturers will be entirely immune to the pressure imposed by major provincial purchasing agencies for additional discounts.

MEXICO: CONSOLIDATED TENDERS SQUEEZING PUBLIC SECTOR PRICES

Manufacturers selling into Mexico’s institutional market have seen prices subjected to growing pressure since the IMSS began handling consolidated tenders on behalf of multiple public purchasing agencies in 2012. Purchasing volumes have risen progressively since then as more agencies have participated in the process, while tendering rules have been refined in a bid to extract additional savings. Nor, while they are clearly exposed to more extreme pressure, have savings been generated exclusively on multi-source drugs. Originators have also been willing to trade price in return for the volumes that tender-based supply contracts guarantee, especially in segments of the market where several poorly differentiated brands are competing for sales.

Tenders for the supply of drugs and other medical inputs to the public sector in 2015 were concluded in December 2014. The number of agencies represented by IMSS in that round of tenders exceeded 40 (up from just 12 in the previous year). They included both major social security institutes (the IMSS itself and the Institute for Social Security and Services for State Workers [Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado], which administers health insurance for public sector workers and their dependents), the state-owned oil company PEMEX, all 21 national institutes of health, and about half of the country’s 32 state healthcare authorities (Mexican Health Review, 2015).

The IMSS reported that consolidated tendering generated savings worth MXN3.9bn ($260m) on the purchase of generic drugs and wound care products. It also said that bulk purchasing of innovative medicines had generated savings worth an additional MXN620m ($41m). Previous contracts had been awarded on a 60/40 basis to the lowest and second-lowest bidders. For 2015, however, the lowest bidders were promised 80% of contracts by volume. Coupled with the anticipated involvement of more states in future tenders, this is expected to drive a further reduction in bid prices for many generics, and for innovative drugs that face competition from other original brands (Mexican Health Review, 2015).

INDONESIA: LOW CEILING PRICES LIMIT INTEREST IN INSTITUTIONAL MARKET SUPPLY

While demand for prescription drugs has risen sharply since the Indonesian government began to roll out its new universal health insurance scheme (JKN; Jaminan Kesehatan Nasional) at the beginning of 2014, institutional purchases are dominated by generics, and most manufacturers say prices are too low for them to compete profitably in the sector (Anggriani et al., 2016).

Prior to the introduction of the JKN, the government drew up a new national formulary (Fornas) and established an electronic tendering system for the supply of drugs on that list. The system is based on an e-Catalogue, which outlines acceptable price ranges for individual products. Companies competing
for the supply of drugs on the formulary are expected to tender bids at prices within those ranges (Depkes, 2015).

Early experience has shown that tenders are decided almost exclusively on price, with little weight accorded to product quality or supply capabilities (Anggriani et al., 2016). More than one-third of all products on the new national formulary are not available in generic form, however, and while funding considerations will limit purchase volumes, originators may be willing to negotiate flexibly on the prices of some listed drugs. The use of these products in the public sector will increase awareness of the brands in question among prescribers and patients, potentially boosting future opportunities in the private market.

SOUTH KOREA: NEW PROVIDER REWARDS SYSTEM DELIVERS A DOUBLE BLOW TO PRICES

The latest changes to South Korea’s drug pricing system will heap further pressure on procurement prices, and are also expected to have a negative impact on volumes being purchased by providers. Introduced in September 2014, the Rewards for Saving Drug Expenditure (RSDE) system offers providers a share of savings generated by purchasing drugs at lower prices, reducing overall drug costs and cutting usage volumes. As such, it encourages a tougher approach to negotiations with suppliers, more widespread use of low-cost generics, and a more conservative approach to prescribing.

The RSDE will deliver a double blow to manufacturers, since it will involve the imposition of reimbursement price cuts for drugs that have been sold to providers at levels below the NHI reimbursement price. An initial round of cuts was implemented under the scheme in March 2016 (IMS Health, 2015).

The RSDE system offers incentives for reducing NHI expenditure on both inpatient and outpatient drugs. As such, it is available to a range of providers, although large public hospitals are expected to deliver the most significant savings (and, as a result, will reap the biggest rewards), reflecting both the type of drugs they prescribe and the volumes at which they purchase medicines.

TURKEY: POOLED HOSPITAL PURCHASING BEGINS TO DRIVE DOWN PROCUREMENT PRICES

Public hospital procurement systems are being overhauled as part of a broader drive to curb spending by the Turkish Social Security Institution (SGK; Sosyal Güvenlik Kurumu). Early indications are that increased tender volumes have already begun to erode prices in the sector (Pharmaceutical Executive, 2015).

Electronic tendering for public hospital supplies was piloted at the beginning of this decade, and is now well established. Tenders were still issued and administered largely at the individual facility level, however, and moves towards consolidated purchasing offered a clear opportunity to generate savings for the SGK. Accordingly, units tasked with the administration of purchasing and stock management for multiple facilities were set up (Pharmaceutical Executive, 2015).

The first consolidated tenders for hospital supply were issued in 2014. There are approximately 100 pooled purchasing units, operating at city level in the country’s largest urban centers, but with
broader geographical responsibilities in less populous areas of the country (Pharmaceutical Executive, 2015). Further consolidation of public procurement could clearly drive additional savings in the long term, but policymakers will monitor the existing system before pursuing such a move, which would pose more complex logistical challenges.

Bibliography


DISTRIBUTION

Import tariffs, discriminatory approaches to registration and pricing, local manufacturing, and foreign ownership rules are among the market access barriers faced by originators importing their brands into the BRIC/MIST markets (Brazil, Russia, India, China, Mexico, Indonesia, South Korea, and Turkey). The physical distribution of drugs can also pose a significant challenge, reflecting complex geographies, testing climatic conditions, the limited nature of transport infrastructures, and – in the institutional market – inefficient, sometimes chaotic state-run distribution networks. Payment issues represent an additional problem for originators selling into some institutional markets.

Like manufacturers, other stakeholders in most BRIC/MIST distribution chains have been affected by policies designed to rein in pharmaceutical spending. With players at both ends of the chain attempting to bolster their own margins, profits generated by wholesalers and distributors have been subjected to a particularly tough squeeze, triggering significant restructuring.

Early efforts by multinationals to penetrate most emerging markets often involved the registration and sale of narrow portfolios, and targeted providers in core, easy-to-reach urban areas. The establishment of broader portfolios and the pursuit of opportunities beyond these core markets have raised a number of additional issues for originators. In large, geographically complex markets these include the ability of manufacturers to retain control over lengthy, multi-layered distribution chains.

Barriers to market access for imported drugs

REGULATORY AND TARIFF BARRIERS

Import tariffs are a basic fact of commercial life for foreign companies operating in the BRIC/MIST markets. These may be reduced or waived where essential drugs cannot be sourced domestically, but with governments in some emerging markets keen to reduce their reliance on imports, duties and other, non-tariff barriers are being raised.

By handing local manufacturers a competitive advantage through preferential tariff structures, approval times, or pricing and procurement mechanisms, policymakers aim to encourage the expansion of domestic pharmaceutical industries. As well as vital sources of low-cost drugs, local manufacturers are also seen as important generators of employment and, in some countries, export revenues.

The imposition of taxes, duties, and non-tariff barriers on imported drugs is also designed to encourage more substantial investment by foreign manufacturers. This has been successful in China, but some other BRIC/MIST markets make relatively unappealing targets for major investment, given the size of other market access challenges they currently pose for originators. Nevertheless, with the scales tipping further in favor of locally manufactured products in countries such as Russia and India, a more substantive local presence may eventually become vital for multinationals with a long-term commitment to these markets.

HEALTHCARE AND TRANSPORT INFRASTRUCTURES
Manufacturers have also been required to weigh additional distribution costs against the returns generated by sales outside of core markets. The sums do not always add up, and poor margins have prevented some companies from pursuing deeper penetration into several BRIC/MIST countries.

Prospects outside core urban markets should improve over the long term, as governments invest not only in the expansion of the public health infrastructure, but also in major transport infrastructure projects that will ease access to currently remote areas. Coupled with rising incomes, these developments should also encourage private providers to broaden their geographical horizons, creating new opportunities for the sale of originator products beyond core urban centers. This trend is already evident in India, where leading private hospital chains are expanding beyond Tier 1 cities (Forbes, 2011).

Constraints on the emergence of these trends remain considerable in some countries, and progress in several will be slow. Recruiting staff to work in public health facilities outside cities has proved a particular sticking point, even where financial incentives have been offered to physicians and other qualified health professionals willing to do so. Sharp disparities between regional income levels pose another formidable barrier to the geographical expansion of demand, especially for originator drugs, in countries such as Brazil. There, opportunities for multinationals remain focused firmly in the south and south-east of the country, and a change in this situation remains difficult to envisage in the foreseeable future.

**COMPLEX DISTRIBUTION CHAINS**

Geographical factors have ruled out the emergence of truly national distributors in several BRIC/MIST markets to date, while first-tier wholesalers often do not offer penetration of rural markets. Where this is the case, products may pass through the hands of several players before they reach local retail outlets or rural hospitals and health centers.

This obviously drives up distribution costs, but also poses additional problems for manufacturers. Multi-layered distribution chains limit their ability to maintain control over the movement of their products to end-users, the conditions under which they are transported, and, sometimes, the price at which they are sold to pharmacies or healthcare providers.

These issues have remained a major problem for manufacturers in India, partly because of the power wielded by the country’s pharmacy trade association (The Hindu Business Line, 2013). The threat of widespread boycotts has forced manufacturers to play largely by the retail association’s rules, limiting their ability to implement more strategic distribution choices or manage discounting policies (PharmaBiz.com, 2015).

Corruption, theft, and counterfeiting also pose a more serious threat in markets with complex, multi-layered distribution chains. Regulators in most BRIC/MIST markets have stepped up efforts to tackle illegal trade in medicines, but it remains a significant problem in several of the eight countries.

Distribution is also problematic in the institutional segments of some BRIC/MIST markets. Again,
efforts to tackle corruption in public procurement have made significant headway, but the physical
distribution of medicines to public hospitals and health centers is often poorly managed. In some
countries, including Indonesia, it remains downright chaotic (Global Fund, 2015).

Institutional markets are often served by specialist wholesalers or logistics providers. In some
countries, the involvement of these players is limited to the supply of state-run depots, however, and
systems for managing the storage and delivery of medicines to individual healthcare facilities are
often inadequate. Typical results include poor storage of medicines, frequent drug stock-outs in public
health facilities, and the widespread existence of date-expired products in public hospitals and health
centers.

Key national developments

BRAZIL: FINANCIAL CRISIS AFFECTING DISTRIBUTION AND SUPPLY; MCKESSON EXITS THE
MARKET

Brazil’s deepening financial crisis has begun to disrupt the public healthcare system (Sistema Único de
Saúde), while budget cuts look set to affect patient access to both specialty drugs and the chronic
medicines distributed free or at heavily subsidized prices under the country's Farmácia Popular
scheme.

The governor of Rio de Janeiro declared in December 2015 that the state's healthcare system was in a
state of emergency, with cash-strapped public hospitals unable to pay staff or purchase equipment
and medicines. In response, the federal health ministry released additional funding for the sector, a
proportion of which was earmarked for settling hospital debts with suppliers (Sinha, 2015).

Payment and budget issues will have implications for both manufacturers and pharmaceutical
wholesalers, affecting sales volumes and exacerbating payment problems, which were already an issue
in the public sector. Wholesaler margins are also being squeezed by pharmacy chains, while plans to
harmonize differential state tax rates threaten the financial future of many small distributors, which
currently profit by selling stocks across state lines (Avalara, 2015). Substantial restructuring of the
wholesale sector could have implications for market access, given the role currently played by small
and mid-sized distributors in servicing remote areas of the country.

McKesson, which had acquired a majority stake in Celesio a year earlier, announced in 2015 that it
planned to divest Celesio’s interests in the Brazilian drug distribution market, which included a
majority stake in one of the country's three leading pharmaceutical wholesalers, Panarello, and the
specialist wholesaler, Oncoprod. A sale to local company SC Participações Empresariais was
announced in February 2016, with McKesson noting that it expected to book an impairment charge of
$70m–90m in connection with the deal (McKesson, 2016).

Supply of the private sector is more robust, partly because both private hospitals and retail
pharmacies are concentrated heavily in the country's major cities. With around a quarter of the
population enrolled in private health plans, this segment of the market will remain a key target for
originators, although coverage rates have declined (ANS, 2016), and could fall further if the economic
climate continues to deteriorate.

RUSSIA: MARGIN SQUEEZE DRIVES DISTRIBUTOR CONSOLIDATION AND COST-CUTTING

Pressure on distributor margins in Russia has intensified, prompting further restructuring in the sector. Finnish company Oriola sold off its Russian distribution business in 2014 (Oriola, 2014), while Imperia Pharma announced its withdrawal from the pharmacy supply market in 2015. Imperia’s retail distribution arm has filed for bankruptcy, and the company will focus exclusively on the delivery of publicly procured medicines in the future (Pharmvestnik, 2015).

This means that 10 leading wholesalers now handle more than 80% of pharmaceutical sales in Russia. Most are operating on slim margins or at a loss, however, and some further consolidation of the market is anticipated (RNC Pharma, 2014).

Several leading wholesalers are owned by parent companies with interests in both pharmaceutical manufacturing and the retail market, and vertical integration has been used as a tool to help prop up margins (The Pharma Letter, 2014). Distributors are attempting to trim costs further by increasing levels of efficiency. Significantly, some wholesalers are also attempting to reduce their exposure to currency risks by handling fewer imported products (Deloitte, 2015). This will have particular implications for multinationals negotiating with distributors to handle original brands in Russia.

INDIA: POWER OF RETAIL LOBBY STILL LIMITS ROOM FOR STRATEGIC MANEUVER

Like other manufacturers, originators targeting retail sector supply are still struggling to combat the power wielded by the All-India Organization of Chemists and Druggists (AIOCD). The organization has effectively blocked consolidation of India’s complex, multi-layered distribution system, stalling the emergence of large, regional distributors and dictating supply terms to manufacturers.

The AIOCD has fallen foul of the Competition Commission on more than one occasion – most recently in December 2013, when it was fined for abuse of a dominant position in the drug distribution market (The Hindu Business Line, 2013). Mindful of the boycotts suffered by those that fail to toe the AIOCD line, manufacturers and distributors remain wary of confronting the organization, however. As a result, most continue to work with multiple distribution partners.

Originators typically employ at least one clearing and forwarding agent (CFA) to handle the logistics of distribution into each state, and work with at least two or three main wholesalers per state (PharmaBiz.com, 2015). Small sub-wholesalers often supply end-users outside major urban centers, adding to the complexity of the distribution market.

Dictating terms of supply in the private hospital sector is easier for originators. Large private hospitals often negotiate directly with CFAs or distributors, cutting wholesalers out of the chain. Some negotiate directly with manufacturers, and while volumes in this sector of the market are limited, originators are often willing to offer preferential terms in order to generate exposure for key brands (CIPHP, 2007).
DUTY EXEMPTIONS WITHDRAWN AS PART OF IMPORT SUBSTITUTION DRIVE

India’s Central Board of Excise and Customs announced the withdrawal of exemptions from import duties for 76 drugs in January 2016, in line with Prime Minister Narendra Modi’s Make in India import substitution campaign. Exemptions for octreotide, somatotropin, and coagulation factor concentrate (VIII and IX) were subsequently reinstated amid concerns surrounding the availability of locally manufactured alternatives. The remaining products on the list – which include recombinant human erythropoietin, filgrastim, and drugs for the treatment of HIV, diabetes, Parkinson’s disease, bacterial infections, arthritis, and glaucoma – will all be subject to customs duties levied at rates of between 5% and 22%, however (Economic Times, 2016).

Multinationals have been lobbying for a reduction in taxes on imported medicines, but appear unlikely to make significant headway if the current government maintains its import substitution drive. Originators claim that while basic import duties on pharmaceuticals average around 10%, effective taxes total almost 20% when other tariffs are taken into account, and that the Indian government collects more in taxes on pharmaceuticals than it spends on medicines (PhRMA, 2016).

CHINA: HEALTH REFORMS AND ANTI-CORRUPTION DRIVE TO TRIGGER DISTRIBUTION SHAKE-UP

Policymakers in China have made clear their desire to clean up the drug distribution business, and to encourage consolidation in a sector renowned for its inflationary impact on drug prices. The push for change will no doubt be stepped up in the wake of the latest developments in the sector, which saw regulators report in March 2016 that they had broken up an illegal vaccine distribution ring alleged to involve at least nine wholesalers (Reuters, 2016).

The sector has witnessed a period of steady consolidation, but around 13,000 companies are still involved in the distribution market, while the three leading wholesalers possess a combined market share of little more than 30%. Outright leader Sinopharm, which has completed more than 80 acquisitions since it floated on the stock exchange in 2009, has seen its share rise from 10% to around 17% (Fitch, 2015).

Originators often strike exclusive agreements with first-tier wholesalers, but products can sometimes pass through the hands of several players before they reach hospitals, clinics, or retail outlets beyond the country’s major urban centers, with each imposing a markup (A.T. Kearney, 2012). Prices have been inflated further by hospitals, which regard medicines as an important revenue stream, but reforms being implemented in this sector aim to remove the profit motive from hospital purchasing and prescribing. If successful, this could have major implications for distributors, which may face less pressure for discounts, but which will have to service a growing retail market.

At the same time, distributors will see their operating costs rise following the introduction of new Good Supply Practice (GSP) standards in the sector. Full implementation of the new requirements was scheduled to take effect at the end of 2015, by which time their introduction had already prompted the exit of some small distribution businesses (Fitch, 2015). Further consolidation is anticipated as GSP standards are policed more closely, encouraging the emergence of a sector populated by fewer, larger, more efficient wholesaling groups.
The government’s 12th Five-Year Plan called for the active support of restructuring in the sector. It aimed to see the eventual emergence of one or two national distributors with annual sales of more than CNY100bn ($15.9bn), and of around 20 regional players, each with annual sales in excess of CNY10bn ($1.6bn) (Deloitte, 2011).

MEXICO: FURTHER TURMOIL AHEAD IN THE WAKE OF PANAMA PAPERS LEAK?

The Mexican drug distribution sector, which has been in a constant state of flux over the past 2–3 years, could be the subject of further upheaval following allegations that the country’s leading wholesaler, Nadro, secretly funded the 2015 purchase of rival distributor Marzam by Dutch investment fund Moench Cooperatif (Montes, 2016). Details of the transaction were reportedly contained in documents leaked from the Panamanian law firm Mossack Fonseca.

Between them, Nadro and Marzam now handle around half of all branded drug sales to retail pharmacies and private hospitals in Mexico. Retailers say drug prices have risen sharply since the deal was closed, and some chains are now refusing to stock certain branded prescription products (Montes, 2016).

The leaked papers also allegedly contain details of price-fixing agreements struck by Nadro with leading pharmaceutical companies. Mexican competition authorities are looking into the allegations, and could open formal investigations, not only into the purchase of Marzam, but also into potential price-fixing activity. The national antitrust commission has the power to annul the transaction if it finds that the deal is in breach of competition laws (Montes, 2016).

Nadro, Marzam, and a third wholesaler, Casa Saba, have traditionally dominated private sector distribution in Mexico, but their hold on the market has been weakened by the emergence of powerful pharmacy chains, some of which now purchase drugs directly from manufacturers. With pressure on wholesaler margins increasing, Saba was teetering on the brink of bankruptcy in 2013. It was acquired by private equity funds in 2014, but its share of the wholesale market had declined significantly by then, with Nadro, Marzam, and some smaller, regional distributors picking up substantial chunks of Saba’s business (The Wall Street Journal, 2016).

Leading private wholesalers are also involved in supply of the institutional market, although most are relatively modest suppliers of major public sector purchasing agencies such as the Social Security Institute (Instituto Mexicano del Seguro Social) and Institute for Social Security and Services for State Workers (Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado). Fármacos Especializados, which ranks fourth in the private wholesale market, is a significant supplier of the institutional market, but the sector is otherwise serviced largely by specialist distributors, including companies such as Equimed del Centro, Savi Distribuciones, Selecciones Medicos, Farmacéuticos Maypo, and Ralca (OECD, 2014).

INDONESIA: GLOBAL FUND AUDIT HIGHLIGHTS INSTITUTIONAL MARKET SHORTCOMINGS

Financial and logistical issues have emerged as major threats to the efficient rollout of Indonesia’s new national health insurance scheme (Jaminan Kesehatan Nasional). The initiative aims to provide
universal access to a range of essential drugs in public health facilities, but distribution and supply problems mean medicines on the list are often not available in practice.

The institutional market is supplied through deliveries to a network of government warehouses, but the management of purchasing, inventory control, distribution, and stocking functions is chaotic. The extent of problems in the sector was underlined by a recent Global Fund audit of grants to Indonesia for the purchase of HIV, tuberculosis, and malaria drugs. Fund inspectors reported weak forecasting and inventory controls in 87% of the warehouses and 40% of the health facilities they visited. Stock-outs of at least one essential drug were found in over half of all warehouses and one-third of health facilities. Date-expired drugs were found in 63% of warehouses and 33% of facilities, while inspections found that 56% of warehouses and 69% of health facilities visited did not adhere to good storage practices (Global Fund, 2015).

Leading domestic manufacturers possess their own distribution arms, some of which also handle the distribution of products on behalf of foreign companies. The state-owned company Kimia Farma is a major player in this regard (Kimia Farma, 2016), while APL and Anugrah Argon Medica are among the leading distributors in the private sector. Some foreign companies possess their own distribution capabilities, although sub-distributors are used widely as a means of penetrating beyond the country's major urban centers.

**SOUTH KOREA: SQUEEZE ON DISTRIBUTOR MARGINS DRIVING CONSOLIDATION**

While it remains highly populated, consolidation of the South Korean drug distribution market is being driven by the combined impact of rising costs and restrictive pricing policies pursued by regulators since the beginning of this decade. The trend has fueled tension between distributors and their principals, with manufacturers attempting to shore up their own margins by trimming distributor payment rates.

Distributors, which pocket percentage-based margins on the turnover of the products they handle, have been particularly critical of multinationals, which they say have limited their margins to 7% or less, compared with figures of 10% or more offered by many local manufacturers. Local distributors have also expressed growing concern over the number of multinationals striking exclusive distribution agreements with the foreign-owned distribution specialist Zuellig Pharma. The Korea Pharmaceutical Distribution Association, which believes the extent of such agreements may violate the Pharmaceutical Affairs Act, has called on regulators to look into the practice (Korea Times, 2014).

As well as dwindling markups, distributors have been hit by rising costs, including expenses associated with the implementation of new traceability requirements. A barcode-based track-and-trace system has been phased in gradually since 2013, and serialization requirements have applied to all drugs since the beginning of 2016. Distributors have struggled to manage the new system, however, reporting high barcode error rates and problems caused by inconsistencies in both the type and placement of barcodes on packaging (KRPIA, 2016). These issues disrupted distribution activity in the early part of 2016.
TURKEY: GOOD DISTRIBUTION PRACTICE TO DRIVE FURTHER CONSOLIDATION OF THE WHOLESALE MARKET

Phase two of Turkey’s EU accession action plan envisages the implementation of new regulations governing pharmaceutical distribution during 2016. Designed to bring national rules into line with EU norms, changes will involve amendments to existing legislation in the field, and the adoption of EU Good Distribution Practice guidelines (MFEUA, 2014).

Compliance with new standards will drive up wholesaler costs. With wholesaler margins already under intense pressure as a result of falling drug prices, this is expected to trigger a period of further consolidation in the drug distribution sector. A degree of restructuring has already been witnessed, but there are still around 200 licensed pharmaceutical wholesalers operating in the country (SED, 2016). Many are small, family-run businesses, and these are the most likely casualties of tighter regulation. Few will represent particularly attractive acquisition targets, and consolidation will largely involve the transfer of business from these small companies to larger players.

Retail market supply is dominated by two large wholesalers and pharmacy co-operatives, but around a dozen smaller distributors still play a significant role in the sector at regional level. Selçuk Ecza Deposu claims an outright leadership position, with its share approaching 40% in value terms by the end of 2015. Hedef Alliance, in which Walgreens Boots Alliance has a controlling stake, is the country’s other leading drug wholesaler, with a market share of approximately 30% (SED, 2016).

Since direct distribution to retail pharmacies is not permitted, both leading players are expected to pick up additional business as a result of further restructuring in the wholesale market. Operating margins in the sector will remain under pressure, however, and this could see either or both of the two market leaders begin to reassess their business models. Changes could include diversification into related healthcare distribution fields, but may also involve the establishment of more added-value services for manufacturing principals.

Bibliography


PRESCRIBING

Population growth, aging, epidemiological trends, and improved access to healthcare have all driven up demand for medicines in emerging markets. Where governments are funding improvements in provision, reforms have been accompanied by the imposition of new or more substantive cost-containment measures. These usually include pricing and reimbursement regulations, but policies aimed at prescribers often also feature.

There is a strong correlation between the availability of government-subsidized medicines and the degree to which prescribing in the public sector is both monitored and regulated. Where outpatient drug subsidies are either limited or non-existent, prescribing outside the hospital sector is often subject to few controls. Indeed, patients in some BRIC/MIST markets (Brazil, Russia, India, China, Mexico, Indonesia, South Korea, and Turkey) are able to purchase a broad range of ethical drugs from pharmacies without the need to consult a physician or present a prescription. Here, while patients may request a product with which they or a family member have been treated in the past, pharmacists often act as de facto prescribers, offering advice on drug choice.

Levels of prescribing freedom are also much greater where physicians are treating patients with private health insurance, partly because prescription drugs often represent a significant income stream for private hospitals. Accordingly, while demand for their products may be limited, these are areas in which originators possess the potential to exert a more significant impact on prescribing decisions.

Although their ability to influence prescribing in the public sector is more limited, the institutional market still remains a key target for manufacturers. This is largely a reflection of the huge potential volumes that can be generated in the sector. Access to the institutional market also has the potential to drive sales in the private sector, however, providing both physicians and patients with direct experience of a product and its benefits.

Shortages of medical specialists

Although a significant proportion of physicians in most BRIC/MIST countries are specialists, few are qualified in the fields that have emerged as major challenges to the health status of patient populations over the past 10–20 years.

Chronic non-communicable conditions such as cancer and cardiovascular disease are now among the leading causes of mortality in most of the eight BRIC/MIST markets. Most medical specialists still practice in areas such as family medicine, internal medicine, pediatrics, or general surgery, however, and shortages of qualified specialists in fields such as oncology and cardiology are commonplace.

Shortages are most acute in the public sector, reflecting the superior salaries and working conditions that private providers can offer to highly trained staff. As a result, while access to free or subsidized treatment of non-communicable diseases is provided by public healthcare systems on paper, it may be limited in practice by the failure of those systems to cope with demand.
In Mexico, 38% of around 259,000 doctors employed in the public sector are specialists. The sector has access to just 1,200 oncology specialists, however, despite the fact that cancer is the country's third biggest killer, claiming more than 80,000 lives every year (Rodríguez, 2014).

**Regulatory controls on prescribers**

Prescribing choice in most BRIC/MIST markets is subject to few direct controls. In some countries this reflects the modest nature of government contributions to drug spending. The political power wielded by the medical profession has enabled physicians to avoid the imposition of stricter controls in other markets, however, while several governments simply lack the resources to monitor prescribing effectively.

Prescribing is subject to closest scrutiny in South Korea. There, the country’s Health Insurance Review & Assessment Service (HIRA) has developed sophisticated IT platforms that enable detailed reviews, not only of medical claims submitted by providers, but also of prescribing activity. Reimbursement is forfeited where physicians have failed to prescribe in line with clinical guidelines, while irrational prescribing can trigger regulatory intervention or reductions in provider reimbursement tariffs (EOHSP, 2009).

Elsewhere, efforts to monitor and/or control prescribing activity more effectively are being pursued in China, Indonesia, and Turkey. Governments in all three of these countries have funded significant improvements in access to subsidized healthcare provision, and are keen to rein in rates of increase in the costs of these programs.

The most significant changes are anticipated in China, where hospital reforms outlined recently by policymakers aim to eliminate profit-driven prescribing and reduce the contribution of drugs to hospital budgets (Fitch, 2015). Physicians in Turkey will also be subject to closer scrutiny as the government there pursues a new rational drug use drive, while prescribing trends in Indonesia will be monitored as part of a bid to limit the cost of rolling out a new national health insurance (NHI) scheme.

Inducements or indirect measures designed to shape prescribing decisions will remain the favored approach by policymakers in most BRIC/MIST markets. These will see the introduction or expansion of initiatives offering financial rewards for rational, cost-effective prescribing, and will also involve restructuring of provider payments. In the hospital setting, flat-sum reimbursement models will be used to limit treatment costs, encouraging more widespread use of low-cost generics at the expense of original brands.

Physicians employed in public health facilities are required to prescribe by international non-proprietary name (INN) in some BRIC/MIST markets. Enforcement of generic prescribing rules is often patchy, however, while exemptions are relatively common.

**Enforcing the prescription status of antibiotics**

Historically, antibiotics have been chronically overprescribed in most BRIC/MIST markets.
Overconsumption has been encouraged further by the ability of patients in some countries to purchase antibiotics freely in pharmacies without presenting a physician's prescription. As a result, microbial resistance is now a significant problem, and governments have begun to impose tighter controls on antibiotic prescribing and dispensing in a bid to preserve the efficacy of key molecules.

Levels of adherence and enforcement vary, but the imposition of more restrictive regulations has had a significant impact on antibiotic prescribing in several BRIC/MIST countries. Efforts to reduce antibiotic consumption are most established in South Korea, where the rate at which they are being prescribed for conditions such as upper respiratory tract infections has declined dramatically (HIRA, 2015).

Tighter regulations governing the prescription and sale of antibiotics in Brazil and Mexico are a more recent development, but have reined in usage rates in both countries (Santa-Ana-Tellez et al., 2013). In China, where almost half of all outpatient prescriptions were being written for antibiotics, the imposition of tighter controls in 2012 has had a similar impact (Currie et al., 2014). Antibiotics are now split into three categories for prescribing purposes, and those products subject to a "special management" classification may no longer be prescribed on an outpatient basis. Finally, new regulations designed to curb both the prescription and sale of antibiotics in Turkey were introduced in 2015.

**Affordability as a barrier to prescribing**

Even where governments fund the majority of costs associated with a drug, percentage-based co-payments may be beyond the pockets of many patients in low-income markets. This can rule out the prescription of an original brand from a newer, more effective class, effectively forcing physicians to prescribe a cheaper, older generic alternative. Patient outcomes often suffer as a result, imposing much higher costs on healthcare systems over the long term. Public sector drug budgets are under growing pressure, however, and persuading policymakers to take a more rounded, long-term view on the provision of fully reimbursed medicines remains a challenge.

In the meantime, affordability continues to exert a significant impact on prescribing decisions – acting as a particular constraint for specialists. In China, more than 40% of pulmonologists surveyed recently described out-of-pocket costs as a major barrier to prescribing choice, despite the fact that most asthma and chronic obstructive pulmonary disease drugs are partially reimbursed by social health insurance schemes (Ribeiro, 2015).

More positive developments are being witnessed in South Korea, where the government is pursuing the provision of more comprehensive reimbursement in four key therapy areas, including cancer treatment. Sharp cuts in patient co-payments towards the cost of several cancer drugs were announced by regulators in February 2016 (see below).

**Key national developments**

**BRAZIL: DEBATE CONTINUES ON “JUDICIALIZATION” OF HEALTH**
Uniquely, the courts have emerged as a significant driver of prescribing activity in Brazil. Patients in their tens of thousands have filed lawsuits in a bid to secure their right to healthcare, which is enshrined in Article 196 of the country’s 1988 constitution (WHO, 2008). With the vast majority of cases settled in favor of plaintiffs, this has inflated federal and state spending on medicines, and will encourage more patients to use legal avenues as a means of gaining access to pharmaceuticals, including innovative new drugs.

Between 2002 and 2009, the number of health-related lawsuits filed against the state health authorities in Rio Grande do Sul alone rose from just over 1,000 to more than 17,000 a year. Almost three-quarters of all lawsuits demanded access to medicines, and by 2008, drugs accessed by patients through the courts accounted for 22% of spending on pharmaceuticals by the state (Biehl et al., 2012).

An analysis of suits filed in Rio Grande do Sul has shown that shortcomings in the healthcare system have been a major driver of the so-called “judicialization” of health. Almost two-thirds of drugs sought by patients who filed lawsuits there during 2009 were already listed on government formularies, and should have been available to the plaintiffs. The study showed that more than a quarter of the most widely requested drugs did not feature on public formularies, however, and policymakers have warned that patients seeking access to high-cost medicines through the courts threaten to undermine funding for the provision of essential drugs used by millions of patients (Biehl et al., 2012).

The problem is unlikely to improve in the near future, given the restrictive approach being pursued by regulators to listings on the country’s high-cost drugs formulary, the specialist pharmaceutical assistance program (CEAF; Componente Especializado da Assistência Farmacêutica), and the fact that public sector drug budgets for 2016 have been trimmed as part of a government-wide cost-cutting exercise (Ministry of Health, 2016). Most lawsuits will continue to involve demands for access to drugs listed on public sector formularies, but patients will also challenge CEAF listing decisions where these have refused access to reimbursement for innovative new drugs. Most will do so by presenting prescriptions written by physicians recommending their treatment with such products.

RUSSIA: TIGHTER CONTROLS COULD PRECEDE NATIONAL REIMBURSEMENT SCHEME

Plans to begin rolling out a national outpatient drug reimbursement scheme in Russia appear to have been put on hold in the face of a sharp economic downturn. Tighter prescribing controls could still be introduced, but events suggest the enforcement of such regulations may not be prioritized until they begin to have a major bearing on reimbursement costs.

The removal of direct reference to a national reimbursement scheme from the final version of the health ministry’s 2013 document outlining a Strategy for Drug Supply to 2025 suggests that, even then, policymakers were rethinking the timetable for its introduction. The document did identify a number of measures designed to encourage rational prescribing, however, and outlined plans to establish an electronic prescribing platform that would enable regulators to monitor physician activity and reimbursement claims more closely (IHS Markit, 2013).
In July 2013, less than six months after the cabinet had rubber-stamped the Ministry of Health’s (MoH’s) strategy document, new rules obliging prescription by INN throughout the public sector were implemented (KPMG, 2013). Few explicit controls had previously been imposed on physicians unless they were treating affiliates of existing drug subsidy schemes, which are limited in terms of their reach.

While it is unclear how strictly generic prescribing requirements have been policed to date, a restrictive approach is anticipated if, as planned, access to outpatient drug benefits is eventually broadened. Moves towards the establishment of an electronic prescribing system are likely to be pursued before then, allowing for detailed scrutiny of physician activity. Stricter prescribing protocols may also be drawn up before a national reimbursement scheme is rolled out, while regulations detailing penalties for irrational or illegal prescribing will be adopted.

INDIA: PRESSURE MOUNTS FOR TIGHTER CONTROLS ON PRESCRIBERS

Long-running calls for tighter regulation of the medical profession in India finally appear to have triggered a reaction. In May 2016, the Supreme Court appointed a three-member committee, headed by the country's former chief justice, which will oversee the much-criticized Medical Council of India for at least a year (The Hindu, 2016).

Meanwhile, the national MoH has drawn up proposed changes to the council’s 2002 regulations that would mandate generic prescribing. Existing regulations call on physicians to prescribe generically “as far as possible.” That rider would disappear if the MoH proposals are adopted, although how effectively regulators would be able to police a mandatory INN prescribing regulation is another question entirely (The Times of India, 2015a).

STATE INITIATIVES CAN TRIGGER MAJOR SHIFTS IN PRESCRIBING TRENDS

In the absence of a stronger lead from the national government, state administrations have spearheaded the procurement, prescription, and dispensing of free or subsidized medicines. This has had a significant impact on demand for medicines and prescribing trends in the private sector as well as in public facilities.

In Rajasthan, where the state established a free drugs scheme in 2011, an Essential Medicines List (EML) was drawn up in 2012. Orders were issued to all public health facilities calling on them to prescribe from the EML wherever possible, to justify the prescription of drugs not on the list, and to prescribe by generic name. A WHO mission to the state found that adherence to these orders was widespread; more than 90% of prescriptions issued in the state’s public health facilities were for drugs on the EML, and were written generically (Holloway, 2013).

Not surprisingly, the availability of free basic medicines triggered a major shift in demand from the private sector to public health facilities. The number of inpatient visits to government health facilities in Rajasthan rose from 200,000 in the year to March 2011 to more than 3 million in the year to March 2014. Over the same period, the number of outpatient visits increased from 25 million to 66 million. Such shifts had a major impact on private providers and pharmacies in the state; private drug
sales in urban areas fell by 15–20%, triggering the closure of some private health centers and retail pharmacies (Holloway, 2013).

The sheer scale of demand for free medicines has posed major financial challenges for state governments. The Rajasthan government announced in August 2014 that its free medicines scheme would in future be available only to beneficiaries of the state’s food aid program (ie the poorest segments of the patient population). In addition, it said free drugs would in future be available only in the outpatient setting (The Times of India, 2015b).

CHINA: HOSPITAL REFORMS COULD TRANSFORM PRESCRIBING PRACTICE

A new drive to reform China’s public hospital sector has potentially major implications for drug manufacturers in general, and for originators in particular. The reforms aim to eliminate profit-driven prescribing in the hospital sector, where more than three-quarters of all drug sales are generated (Fitch, 2015). With providers also being scrutinized more closely as part of a crackdown on corruption, the changes could transform prescribing practice.

With government funds accounting for less than 10% of their revenue, public hospitals rely heavily on profits from the sale of drugs and the provision of other medical services (Guan et al., 2016). Until now, they have been permitted to impose a 15% markup on prescription drugs. This has driven widespread overprescribing, and has actively encouraged the purchase, prescription, and sale of costlier drugs, including off-patent brands as well as patented originators (Fitch, 2015).

Figure 14: Contributions to public hospital revenues in China

![Figure 14: Contributions to public hospital revenues in China](Source: Guan et al., 2016; Wang, 2015)
On average, drug sales currently account for around 40% of public hospital revenues (Guan et al., 2016). The reforms, which have already been piloted in parts of the country, aim to cap that figure at 25–30%, partly through the imposition of a “zero markup” rule designed to remove the profit motive from the purchase, prescription, and sale of drugs. Where the reforms have been piloted, they have had a significant impact on hospital prescribing trends, driving a shift from the use of patent-expired brands to locally manufactured generics.

Hospitals are understandably anxious about the impact of the reforms on their finances, and major public hospitals in particular will resist change. Implementation of the reforms is likely to be gradual as a result, and the success of the policy may ultimately depend on the willingness of the government to provide more financial support for public hospitals (Fitch, 2015). Coupled with a drive to root out corrupt practices, it could have a fundamental impact on hospital prescribing trends, however, encouraging more cost-conscious prescribing choices where treatment with multi-source drugs is concerned.

If change in the sector plays out as policymakers intend, originators will be forced to overhaul their existing business models in China, devoting fewer resources to patent-expired brands and focusing their efforts on the development and registration of innovative new drugs. This means it will be vital for multinationals to secure improvements in the efficiency of the drug registration process, and in the current pricing and reimbursement framework.

Manufacturers may also have to deal with some unintended consequences of the hospital reform process, examples of which are already apparent. Unable to mark up drug prices, hospitals are likely to push for alternative incentives to purchase from individual manufacturers, including rebates or less conventional inducements.

It emerged in January 2013 that one major hospital in Jiangsu province had requested the payment by manufacturers of a “deposit” equivalent in value to 8% of their annual sales through the facility. When some companies refused to make such payments, the hospital suspended purchases of products from eight multinationals, including high-profile brands such as Pfizer’s statin Lipitor (atorvastatin calcium), and Roche’s cancer drug Xeloda (capecitabine). Its boycott was lifted soon after the matter became public, but settling the spat involved the provision by at least one multinational of more generous payment terms for the hospital at the center of the dispute (Wang, 2016).

MEXICO: RESTRICTIVE PUBLIC SECTOR POLICIES CONTINUE TO FRUSTRATE ORIGINATORS

With both of Mexico’s two social security institutes pursuing an increasingly restrictive approach to formulary listings and reimbursement conditions, originators have found it hard to generate prescriptions for innovative new drugs in the public sector. Opportunities in the private sector also remain limited, however, with the latest figures showing that the number of patients with private health insurance cover has leveled off at fewer than 9 million, or just 7% of the population (OECD, 2016).

Social security affiliates often face lengthy waits in Social Security Institute (IMSS; Instituto...
Mexicano del Seguro Social) or Institute for Social Security and Services for State Workers (ISSSTE; Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado) health facilities, where physician prescribing choices are governed by formulary listings and by prescribing protocols that aim to limit drug spending by the two institutes. Where drugs are prescribed on an outpatient basis, they are only reimbursed where patients obtain them from IMSS or ISSSTE dispensaries. Since this can involve further queuing, many social security affiliates prefer to purchase outpatient medicines on an out-of-pocket basis from retail pharmacies, and cash payments are responsible for the bulk of the country’s national spending on medicines.

Social security affiliates are more willing to endure lengthy waits in overcrowded facilities where their treatment involves the use of more expensive prescription drugs. Few innovative new medicines have been listed on public formularies over the past 3-4 years, however, limiting prescriber and patient choices (IMS Health, 2014). Demand for these products may be limited in the self-pay and private health insurance sectors, but these still represent the best early targets for originators awaiting access for new drugs to the country’s biggest public formularies.

INDONESIA: NHI DRIVING A SHIFT IN PRESCRIBING TRENDS

Aware that the establishment of a universal health insurance system would pose huge financial challenges, policymakers in Indonesia implemented a series of measures designed to curb NHI drug spending before they began rolling out the scheme at the beginning of 2014. These included the creation of an NHI drug formulary, a prescription monitoring initiative, and, crucially, the introduction of a flat-sum hospital payment mechanism (The Jakarta Post, 2014).

The aim of the measures was to encourage a more harmonized, cost-conscious approach to prescribing in the public sector where, notwithstanding previous efforts to encourage generic prescribing, public hospital physicians had continued to prescribe widely by brand name. Early evidence indicates that the new measures had an immediate impact, triggering a noticeable shift towards more widespread prescribing by generic name (Muliawan, 2015).

While the NHI scheme involves the payment of primary care providers along capitation lines, hospitals are being reimbursed using a variation of the diagnosis-related group (DRG) model known as Indonesia Case-Based Groups (INA-CBGs) (EIU, 2015). Since tariffs include drug as well as treatment costs, this has encouraged more widespread generic prescribing.

The shift away from the prescription of branded drugs in hospitals may gather pace if early problems being faced by providers are not resolved. Regulators were forced to adjust a number of hospital tariffs during the first 12 months of the NHI rollout process, but hospitals have also reported issues surrounding the late receipt of payments for the treatment of NHI affiliates (EIU, 2015).

SOUTH KOREA: BRIGHTER PROSPECTS FOR ORIGINATORS IN SOME KEY DISEASE AREAS

Original brands will be prescribed more widely for the treatment of conditions in four key disease areas where policymakers are pursuing more comprehensive coverage by South Korea’s NHI system. With reimbursement levels for some cancer and cardiovascular drugs being stepped up, more patients...
will be able to afford treatment with innovative products. Some original brands will also be prescribed more widely following amendments to NHI prescribing guidelines, which will enable their use as first-rather than second-line treatments.

In February 2016, the Ministry of Health and Welfare increased rates of reimbursement for a number of drugs used in the treatment of pancreatic cancer, chronic myeloid leukemia (CML), soft tissue sarcoma, and lymphoma. Major beneficiaries will include Celgene’s metastatic pancreatic cancer drug Abraxane (paclitaxel), for which annual patient costs will fall from around KRW13m ($11,488) to just KRW600,000 ($530) as a result of the move (Scrip, 2016).

Local company Il-Yang Pharmaceutical’s chronic myeloid leukemia drug Supect (radotinib) will be reimbursed as a first-line therapy, with annual patient co-payments falling from approximately KRW20m ($17,673) to just KRW1m ($884). NHI subsidies have also been ramped up for Eli Lilly’s Gemzar (gemcitabine) plus Taxotere (docetaxel) in the treatment of soft tissue sarcoma, and for gemcitabine in combination with Genentech’s Rituxan (rituximab) in the treatment of B-cell lymphoma (Scirp, 2016).

**BUT HIRA MAINTAINS ITS GRIP ON OVERALL PRESCRIBING COSTS**

The outlook for many other innovative drugs remains less rosy, with regulators clearly determined to maintain their grip on NHI drug spending. The Rewards for Saving Drug Expenditure (RSDE) scheme, introduced in September 2014, is the latest in a stream of measures designed to limit the impact of prescribing activity on NHI reimbursement costs. Like a number of existing initiatives, the scheme offers financial incentives to providers that reduce drug costs. The RSDE encourages hospitals to negotiate more aggressively on purchase prices, but will also reward savings generated by more widespread generic prescribing and reductions in overall drug use.

Regulators already have a firm grip on prescribing, which has been imposed largely by the HIRA. The service uses sophisticated electronic systems to review NHI medical claims, assess treatment quality, and provide real-time drug utilization reviews. These enable detailed scrutiny of prescribing patterns, which are investigated wherever significant anomalies are uncovered (HIRA, 2015).

The HIRA exerts a broad level of control over NHI prescribing through the publication of clinical guidelines, with which providers must comply in order to obtain reimbursement for the 1.4 billion medical claims they submit every year. These restrict the prescribing of many innovative medicines on the NHI reimbursement list, often through the identification of tightly focused patient populations and their indication as second- or third-line treatments.

Established cost-containment initiatives include a prescription-cost incentives program, under which providers may retain a proportion of savings generated by cost-effective prescribing, and a value incentive program, which offers rewards for the cost-effective treatment of conditions such as hypertension and diabetes, but which also penalizes providers whose performance does not meet required standards (HIRA, 2013).
HIRA guidelines, monitoring activity and the availability of provider incentives, have had a significant impact on prescribing trends. Between 2002 and 2013, the average number of drugs included on an NHI prescription fell from 4.32 to 3.76. Over the same period, the antibiotic prescription rate for patients with upper respiratory tract infections fell from more than 73% to less than 45%, while the proportion of outpatient prescriptions containing injectable drugs declined from almost 39% to 19% (HIRA, 2015).

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<th>Table 15: Impacts of cost-effective prescribing initiatives in South Korea, 2002–13</th>
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<td>Antibiotic prescription rate for URT infections (%)</td>
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<td>Proportion of outpatient scripts containing injectables (%)</td>
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<td>Average number of drugs per NHI prescription</td>
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NHI = national health insurance; URT = upper respiratory tract

Source: HIRA, 2015

TURKEY: GOVERNMENT STEPS UP "RATIONAL USE" DRIVE

Public sector drug spending surged in Turkey following the rollout of its universal health insurance scheme, but efforts to rein in pharmaceutical costs have focused largely on the use of price controls rather than the imposition of stricter controls on prescribers. Signs that physicians will be scrutinized more closely have begun to emerge, however, most notably in the shape of a new rational drug use action plan unveiled in 2014 (MoH, 2014).

Covering the period to 2017, the plan targets the introduction of a range of measures aimed at physicians. These will see prescription monitoring stepped up, while a concerted drive to educate physicians more effectively will also be pursued. Clinical guidelines will be drawn up, a treatment decision support system will be established, and prescribing activity will be monitored. Significantly, the plan also calls for the development of performance criteria, and the establishment of incentives designed to encourage more rational prescribing (MoH, 2014).

Existing controls on prescribers are limited, while the enforcement of prescription regulations has been lax. Fines for pharmacies dispensing antibiotics without a prescription were introduced as recently as the final quarter of 2015. Rational prescribing of antibiotics, which feature on almost one-third of all prescriptions, and which generate 14% of all spending on drug reimbursement, will be a priority (Scrip, 2015).
While physicians may have remained largely free from constraints on prescribing choice to date, electronic prescribing has been mandatory since January 2013. The e-prescribing initiative is part of a broader e-health program that involves the establishment of electronic health records, and that will enable detailed analysis of health data during the development of policies designed to improve the quality and efficiency of provision. Analysis of prescription data will be used to determine the qualification of individual physicians or provider organizations for rational prescribing incentives.

The number of reimbursable prescriptions dispensed in pharmacies jumped by 10% to more than 339 million in 2011. Prescription volumes have plateaued since then, however, and fell back marginally (-0.2%) to 337.4 million in 2014. Price controls have kept prescription costs firmly in check, and while the average cost per script rose by 10% in 2014, it was still marginally lower than figures reported in 2010 (SGK, 2015).

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PROMOTION AND MARKETING

Physicians in many emerging markets have traditionally been subject to few explicit controls on prescribing choice. In the absence of such restrictions, manufacturers have been able to exert a significant impact on prescribing trends through heavy promotion of their brands.

In some emerging markets (notably China), providers still rely heavily on profits from the purchase, prescription, and sale of medicines within their premises. Where prescribing and dispensing functions have not been separated, and where drug benefits are either limited or non-existent, profit-driven prescribing is a feature of the outpatient as well as the inpatient sector.

Since competition for shares of emerging pharmaceutical markets is often intense, this situation has been exploited by providers and suppliers alike. As a result, widespread overtreatment by providers and the engagement by some manufacturers in unethical promotional activity are both commonplace. This has driven up pharmaceutical expenditure, inflating costs borne by patients and payers.

Where governments are pursuing the expansion or improvement of access to subsidized healthcare provision, reining in prescribing costs is now a priority. While this has often involved the imposition of more explicit controls on physicians, policymakers are also keen to limit the influence of manufacturers on prescribing decisions. Promotional activity is being scrutinized more closely as a result, while explicit regulations governing the way manufacturers and their representatives interact with physicians are also being imposed.

Promotion as a market access tool

Original brands often enjoy lengthy lifecycles in the BRIC/MIST countries (Brazil, Russia, India, China, Mexico, Indonesia, South Korea, and Turkey). Traditionally, this has reflected widespread doubts surrounding the quality, safety, and efficacy of low-cost, often poorly regulated generics. The imposition of tighter regulations on manufacturers and the establishment of more aggressive pharmaceutical cost-containment measures by policymakers have seen generics emerge as a more potent post-patent threat to original brands, however. With regulatory and, in some BRIC/MIST countries, reimbursement procedures delaying market access for new drugs, this means it has become increasingly important to maximize early sales.

In a bid to achieve this goal, originators have begun to employ marketing strategies that reach further back into the development phase of new drugs being commercialized in the BRIC/MIST countries. Local clinical trials, which in any case are a prerequisite for registration in several of the eight markets, are being tailored increasingly to expose key opinion leaders within the medical profession to new drugs. Where appropriate, they are also being used to generate local pharmacoeconomic and cost-effectiveness data that can be used to support applications for reimbursement.

Once marketing approval has been obtained, heavy physician detailing has traditionally been the key to generating prescriptions for new drugs in emerging markets. However, this strategy is complicated in some BRIC/MIST countries by the ability of patients to purchase many prescription drugs through...
retail pharmacies without the need to consult a doctor. As a result, multinationals have been forced to devote a proportion of their promotional budgets to retailer-targeted activity.

Affordability poses an additional challenge for innovative new drugs. The widespread absence of outpatient drug benefits means this is a virtually universal consideration where products indicated for use outside the hospital setting are concerned. Even hospital co-payments may be beyond the pockets of many patients, however, and originators have been forced to adopt more flexible strategies for new drugs. These have included the establishment of country-specific prices or innovative patient payment mechanisms, but also involve the provision of patient access programs and voucher schemes.

Regulatory controls on promotion and marketing are being stepped up

The degree to which manufacturers are able to influence physician prescribing decisions has long been an issue of concern for regulators in emerging markets. It has become a policy priority in countries where governments are subsidizing pharmaceutical costs more widely, but is also the subject of growing debate in markets where patients foot the majority of the drug spending bill.

New regulations governing promotional activity have been introduced in several BRIC/MIST countries since the beginning of this decade. These have imposed more explicit, more restrictive controls in areas such as the provision by manufacturers of drug samples, gifts, and hospitality for members of the medical profession. Prescribing activity is also being scrutinized more closely where systems and regulatory resources allow, while whistleblowing is being encouraged in a bid to uncover unethical behavior on the part of both manufacturers and physicians.

Physician-targeted promotion is not the only aspect of manufacturer activity that has come under the spotlight. In the face of evidence that unethical practices have been employed by some companies to help "oil the wheels" of registration, reimbursement, and procurement procedures, interactions between manufacturers and regulators are the subject of growing scrutiny. This has triggered the introduction of new rules designed to increase the transparency of these procedures, and to root out corruption. In some countries, including China, Russia, and Brazil, it has driven the establishment of much broader anti-corruption laws.

Where more explicit regulatory controls have not been introduced, originators and leading local manufacturers are generally bound by ethics codes governing promotional activity. For multinationals, these are closely aligned with global codes developed by the industry. Leading domestic companies are usually signatories to separate codes developed by national industry associations, but smaller local producers are often unfettered by such constraints.

While this has driven calls for the establishment of a more level playing field, recent events in several BRIC/MIST markets show that higher-profile companies, including multinationals, have breached not only promotional codes of practice, but also anti-corruption laws. At the very least, this highlights the need for manufacturers to strengthen internal compliance mechanisms. In some cases, there is clear evidence that breaches were not committed by a few "bad apples," and that corrupt practices were either known to or even encouraged by some senior executives. These have been the subject of
widespread publicity that appears sure to trigger the introduction of more concerted anti-corruption drives, involving more effective scrutiny of promotional activity and the imposition of tougher penalties for those found to have breached regulations.

Multinational transgressors also face potential penalties imposed by governments in their own jurisdictions. Eli Lilly, Pfizer, Bristol-Myers Squibb, and Johnson & Johnson are among those to have made multi-million dollar payments in settlement of charges brought under the US Foreign Corrupt Practices Act (FCPA) since the beginning of this decade (Pharmaceutical Compliance Monitor, 2015). Novartis joined that list in March 2016, paying out $25m to settle charges that it had violated FCPA provisions by making illegal payments to healthcare providers in China. The charges alleged that employees at two Novartis subsidiaries in China gave money, gifts, vacations, and entertainment to healthcare professionals in Chinese hospitals between 2009 and 2011 (Bloomberg, 2016).

**Key national developments**

**BRAZIL: CLEAN COMPANIES ACT CLAIMS PHARMA VICTIM**

While the federal police investigation into money laundering and corruption may now be focused primarily on Brazil’s state-owned oil company, Petrobras, early results of the probe – dubbed Operation Car Wash – included revelations of corrupt practice within the country’s health sector. Attention focused specifically on a technology transfer deal negotiated by the Ministry of Health and local company Labogen, under which Labogen would have received payment for the supply of the erectile dysfunction drug sildenafil to public health facilities over a period of several years (Pharmaceutical Compliance Monitor, 2014).

Known as Productive Development Partnerships (PDPs), such agreements are part of a government push to expand the production capabilities of state-owned manufacturing laboratories. Multinationals, which have seen most of their PDP applications rejected in favor of deals with local manufacturers, may be forgiven for wondering how other, similar transactions have been negotiated.

While Operation Car Wash has since claimed a series of much bigger commercial and political scalps, Labogen became the first company to be charged under Brazil’s new anti-corruption law (Pharmaceutical Compliance Monitor, 2014). Implemented in January 2014, and known as the Clean Companies Act, the law outlines civil and administrative sanctions for all private companies found guilty of bribing public officials. These can include fines equivalent to 20% of turnover and, potentially, the suspension or dissolution of companies found to be in breach of the law (Scrip, 2013).

Significantly, while more lenient punishments may be meted out to companies that have implemented internal systems designed to combat bribery, the existence of such initiatives does not constitute grounds for a statutory defense to prosecution under the law (Scrip, 2013). This means it will be essential for drug manufacturers, which deal with government officials on a regular basis, to review compliance policies and monitor adherence to such procedures closely.

**RUSSIA: NEW RULES FOCUS ON RELATIONSHIPS BETWEEN MANUFACTURERS AND PHYSICIANS**
New restrictions on interaction between members of the medical profession and drug manufacturers were outlined in legislation ratified by Russian lawmakers in 2011 and 2013. Separately, members of the Association of International Pharmaceutical Manufacturers, which represents research-based manufacturers in Russia, adopted a new promotional ethics code in 2013.

The Federal Antimonopoly Service, which has long been critical of the influence it believes manufacturers have over physician prescribing, was the main architect of Federal Law 323, which came into force on 21 November 2011. In its original form, the legislation would have had a major impact on the ability of manufacturers to interact with prescribers. Several provisions contained in early drafts were either watered down or removed from final texts, however (Belozertseva, 2011). Some provisions contained in the 2011 law were clarified two years later, while Federal Law 317 of November 2013 also required the disclosure by manufacturers of information on their involvement in, or funding of, events aimed at health professionals (Dentons, 2014).

The 2011 law prohibits doctors from accepting gifts or money from manufacturers, including payments for entertainment or travel. It also rules out the provision of drug samples for use in patients, and imposes limits on representative visits to doctors. As a result, manufacturer representatives may only visit a physician’s office during working hours to discuss their involvement in clinical trials, to collect information on drug side effects, or to improve the professional skills of practitioners. This means traditional detailing calls must take place elsewhere, and outside office hours (Belozertseva, 2011). Although it is unclear how closely these rules are being monitored, strict compliance with the new laws could drive a shift in promotional activity, with a larger proportion of resources being directed at key account management rather than the detailing of individual physicians.

INDIA: MARKETING CODE TO BECOME MANDATORY FOR MANUFACTURERS

After years of procrastination, the Indian government is set to impose a mandatory code of marketing ethics on drug manufacturers operating in the country. The move was confirmed by the Minister of State for Chemicals and Fertilizers, Hansraj Gangaram, in March 2016 (The Economic Times, 2016). The ability of the authorities to enforce the code effectively remains open to debate, although the potential threat posed by whistleblowers may help to encourage compliance.

The ministry shelved plans to introduce a mandatory code five years ago in the face of widespread opposition from the industry, but new guidance was outlined in a Uniform Code of Pharmaceutical Marketing Practices drawn up by the Department of Pharmaceuticals at the beginning of 2015. Regulators warned at the time that failure to observe the code voluntarily may result in its imposition on a statutory basis (PharmaBiz.com, 2014). Predictably, manufacturers showed little interest in the initiative, and so will now be required by law to comply with the code’s provisions.

Manufacturers will seek clarification of some measures contained in the code, and existing texts are likely to be amended in a statutory version. Enforcement procedures and penalties for breaches of the code are also likely to be fleshed out in more detail. In its current form, the code bans the provision of product samples, except to qualified physicians, who may accept samples containing prescribed
dosages for required courses of treatment in up to three patients. The provision of gifts, cash, or equivalents to physicians is prohibited, while limits on the payment of travel expenses for doctors attending scientific events are imposed. Funding to compensate physicians for time spent attending such events is not permitted (Livemint, 2015).

**CHINA: ANTI-CORRUPTION DRIVE RESHAPING PROMOTIONAL STRATEGIES**

The promotion landscape in China has altered dramatically since 2013, when the government launched a new crackdown on bribery and corruption. The crackdown was announced shortly after the authorities began investigating claims that employees of GlaxoSmithKline had engaged in the widespread bribery of hospitals and doctors. Having pleaded guilty, the company was fined almost $500m in 2014, while five GlaxoSmithKline staff, including the British former head of its Chinese operations, were handed suspended jail sentences (Fierce Pharma, 2014).

In the meantime, the authorities announced two new measures designed to combat unethical conduct in the healthcare sector. Published in December 2013, these comprised a set of rules governing the behavior of physicians and healthcare providers, and new penalties for companies found guilty of corrupt or unethical conduct. Both built on existing regulations, but each was more explicit than previous versions, while sanctions for those found in breach of anti-corruption rules were increased (Sidley, 2014).

Measures aimed at physicians and healthcare institutions were outlined in the Nine Prohibitions to Strengthen Ethical Conduct in the Healthcare Industry. Where interactions with manufacturers are concerned, these forbid doctors from accepting bribes, rebates, or other improper benefits, and from attending entertainment events organized or funded by drug companies (Sidley, 2014).

Under new Rules on the Establishment of Commercial Bribery Records for the Purchase and Distribution of Medicine, manufacturers and other suppliers found guilty of unethical conduct must be blacklisted by provincial health authorities. This means they are excluded for a period of two years from competitive tenders issued in the province where an offence was committed. A list of blacklisted companies will be maintained by the National Health and Family Planning Commission, and other provinces may reduce the bidding scores of companies on the list. Repeat offenders face potentially much tougher sanctions. Specifically, any company blacklisted on two occasions within a five-year period will be suspended from the supply of state-run health facilities across the entire country for two years (Ropes & Gray, 2014).

Legal experts say language in parts of both the “nine prohibitions” and blacklisting documents is ambiguous, and manufacturers have struggled to gauge exactly where the line between acceptable and unacceptable interaction with physicians lies (Ropes & Gray, 2014). Given the serious implications of blacklisting, however, most have toed a cautious line to date.

The crackdown on unethical behavior has forced originators operating in China to review and strengthen compliance systems. Enforcing these systems rigorously will pose a challenge, however, given the size of sales forces employed by some multinationals in China, and the traditionally
ubiquitous use of gifts and other inducements to drive sales and prescription volumes in the country.

MEXICO: ORIGINATORS BATTLING RETAIL MARKET DYNAMICS AND FORMULARY LISTING TRENDS

Multinationals have found it increasingly difficult to generate sales of original brands in Mexico. Generics have posed a growing threat to sales of patent-expired brands in the retail market, while originators have struggled to get new drugs listed on major public formularies.

Retail market dynamics have shifted dramatically since the beginning of this decade, reflecting the establishment by pharmacy chains of retail-based physician offices. These are a significant driver of prescriptions that are fulfilled with pharmacy own-label generics, which have captured substantial shares of the retail market. With chains limiting or preventing access to retail-based physicians by representatives of third-party manufacturers, promoting branded outpatient drugs has become more difficult (Pharma Boardroom, 2014).

Generating prescriptions for patented brands has also become more of a challenge, with both of the country's social security institutes – the Social Security Institute (IMSS; Instituto Mexicano del Seguro Social) and Institute for Social Security and Services for State Workers (Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado) – pursuing a more restrictive approach to formulary listings. Legal action by patients seeking access to new drugs not listed on these formularies could potentially emerge as a driver of prescriptions for such products, as it has in Brazil. Evidence to date suggests that Mexican courts will be more sympathetic to public payers, however. Certainly, it appears they will not be required to fund treatment with products not included on the country's national formulary. The IMSS was sued by a patient seeking treatment with Soliris (eculizumab; Alexion) in 2014, but the court ruled in favor of the institute, judging that it was obliged to fund treatment only if a drug was listed on the Cuadro Básico (Goldberg Arnold et al., 2015).

INDONESIA: NEW GOVERNMENT EMBARKS ON ANTI-CORRUPTION DRIVE

The new government elected in Indonesia during 2014 has published a stream of measures designed to tackle corruption, which has long been pervasive throughout the country. While it remains to be seen how effective these will be, the Corruption Eradication Commission (KPK; Komisi Pemberantasan Korupsi) said in September 2015 that it had pursued 47 prosecutions, 25 of which had resulted in convictions (Lexology, 2016).

In the healthcare sector, where local media reports have alleged widespread corruption involving pharmaceutical manufacturers and the medical profession, the KPK signed an eight-point anti-corruption agreement with a range of stakeholders in February 2016. The accord aims to improve the transparency of interactions between drug companies and doctors, ruling out the provision of incentives designed to influence prescribing decisions (Baker & McKenzie, 2016a).

Unethical inducements offered to prescribers have remained a problem despite the fact that doctors and pharmaceutical manufacturers have long been signatories to codes of promotional practice. The IPMG, which represents foreign research-based companies operating in Indonesia, updated its existing
code in 2015, tightening rules governing the sponsorship of health professionals and interactions with
government officials. The latter is also the subject of a new Ministry of Health regulation (14/2014)
implemented during 2014 (IPMG, 2015).

Regulations limiting access to tax deductions on promotional spending by pharmaceutical companies
have been in place since the beginning of this decade. Capped at 2% of total sales or IDR25bn
($1.9m), these act as a disincentive for originators to invest in the registration and marketing of

**SOUTH KOREA: REGULATORS RAMP UP EFFORTS TO TACKLE ILLEGAL REBATES**

Novartis, which is among several multinationals to have been fined by South Korean regulators for
engaging in illegal rebating, is at the center of a new probe that saw its Seoul offices raided by the
authorities in February 2016 (Fierce Pharma, 2016). In an April 2016 US regulatory filing, Novartis
confirmed that the Seoul Western District Prosecutor had initiated a criminal investigation into
allegations that the company had used medical journals to provide inappropriate economic benefits to
healthcare professionals (Novartis, 2016).

Rebating by manufacturers mushroomed in South Korea following the separation of prescribing and
dispensing functions, which made it harder for companies to generate prescriptions for their brands.
Companies found guilty of offering illegal inducements to prescribers can be fined, and may see the
reimbursement price of their products cut (The Korea Times, 2012).

Efforts to tackle the provision of illegal inducements were stepped up in 2010, when new regulations,
known as the "dual punishment" system, introduced penalties for engaging in the practice on
physicians and providers as well as suppliers. Penalties for those found guilty of involvement in illegal
rebating were increased in 2014 through the introduction of a “two-out” system, which can see
repeat offenders or those found guilty of major transgressions face the permanent removal of their
products from the reimbursement list (Lex Mundi, 2016).

The country's Health Insurance Review & Assessment Service monitors prescribing activity closely,
while whistleblowing is actively encouraged by regulators as part of their drive to root out illegal
rebates. Coupled with the introduction of tougher penalties, the news that Novartis is being
investigated by the authorities will prompt other multinationals to review existing compliance
initiatives.

**TURKEY: TIGHTER REGULATIONS INCLUDE SALES REP CERTIFICATION SCHEME**

Rules governing the promotion of pharmaceutical products in Turkey are being aligned progressively
with EU norms. The most recent major changes, outlined in new regulations published during the final
quarter of 2012, imposed significant new limits on promotional activity. These include limits on the
value of promotional materials, sponsorship, donations, and expenses offered to physicians or
providers. Stricter limits on the provision of free samples have also been imposed. Since the beginning
of 2013, the value of free samples may not exceed 5% of a product's total sales in the first two years
following its launch. That figure falls to 3% in the third, fourth, and fifth years, and to 1% thereafter
The 2012 regulation also called on public hospital managers to limit access by sales representatives to their physicians, and ushered in a new sales rep training and certification scheme. Under the new scheme, company representatives visiting health professionals must either possess a university-level promotion and marketing qualification or have passed an examination set by the Ministry of Health. From January 2019, they will also be required to hold a valid accreditation certificate (Baker & McKenzie, 2016b).

Costs associated with the training and qualification of sales reps will drive up promotional spending by manufacturers at a time when their margins are already under strong downward pressure. Sanctions imposed for breaches of the new requirements mean compliance will be essential, however. Repeat offences can trigger the suspension of promotional activity for periods of up to 12 months (Baker & McKenzie, 2016b). With access to hospital prescribers also being limited, originators will shift towards more broad-based promotional strategies, communicating with physicians through electronic channels as well as face-to-face detailing.

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MARKET ACCESS OUTLOOK IN THE BRIC/MIST MARKETS

The market access climate in BRIC/MIST markets (Brazil, Russia, India, China, Mexico, Indonesia, South Korea, and Turkey) is in a state of flux. Change is being driven by factors that extend far beyond government healthcare policy goals, and is being influenced by a growing range of social, financial, and political pressures exerted at regional and global as well as national level.

Success in these highly dynamic markets will depend not just on the product offerings that originators can deliver, but also on their ability to exhibit a greater degree of flexibility and patience than has traditionally been the case. Flexibility will be vital to navigate healthcare systems and regulatory frameworks that are less clearly defined than those in developed markets, and that are prone to sudden, less explicitly signaled change. Patience will also be essential for originators attempting to unlock the huge untapped potential that exists in most BRIC/MIST markets. This will require a willingness on the part of multinationals to play a longer game in which, while rewards may be slow to materialize, the potential scale of eventual returns will be worth the wait.

Maintaining levels of commitment will be particularly important through the remainder of this decade, during which time the challenges faced by multinationals in some BRIC/MIST markets may outweigh new opportunities. Healthcare financing issues will be the main driver of these challenges, which will include the imposition of pricing, reimbursement, and prescribing regulations designed to keep the lid on pharmaceutical spending. But BRIC/MIST governments are under growing pressure to improve access to subsidized healthcare, including innovative new medicines, and most will do so as and when an improvement in their economic circumstances permits.

An eventual return to stronger economic growth will also drive up patient spending on medicines, rendering original brands more affordable to a larger proportion of BRIC/MIST populations. With patients still footing a substantial proportion of national drug spending bills in most of the eight BRIC/MIST markets, this will act as a significant driver of demand for originator products. Rising incomes will also drive up demand for private health insurance, as well as out-of-pocket spending on treatment in private clinics and hospitals.

Key trends

Although developments in individual countries vary, a number of common trends are evident in the BRIC/MIST markets. Generally (though not exclusively), these bode well for improvements in levels of intellectual property (IP) protection, and in the efficiency of drug development and registration procedures. Pricing and reimbursement trends are less positive, however, while the ability of foreign companies to service some BRIC/MIST markets effectively through imports is under threat. And though investment in local manufacturing capabilities could eliminate that problem, outstanding IP protection issues mean multinationals are still reluctant to go down the local manufacturing route.

Key developments at country level in each BRIC/MIST market are outlined later in this chapter. Broader trends in the main areas that impinge on the market access climate across the eight countries are as follows:
- IP protection – World Trade Organization commitments and pressure exerted unilaterally by major trading partners (notably the US) are both driving gradual improvements in the IP protection sector. Ineffective patent protection mechanisms and poor data protection are among the main outstanding issues troubling originators. In low-income markets such as India and Indonesia, concerns surrounding the availability of affordable drugs and the fate of local manufacturers represent additional barriers to the introduction of stronger IP protection frameworks. Compulsory licenses for the generic supply of patented drugs have been issued by governments in both of these markets, and the status of other patents is potentially at risk.

- Clinical trials – Regulators in several BRIC/MIST markets have taken steps to expedite clinical trial approval procedures. Local trial requirements have also been relaxed for orphan drugs and, in some countries, other new products targeting serious, life-threatening diseases. Further improvements in the clinical research climate will be witnessed in countries where governments are keen to encourage foreign investment in R&D. Efforts to strengthen and expand public health infrastructures and to recruit more qualified staff will also improve clinical research capabilities.

- Drug registration – Drug approval procedures have been overhauled or are being reformed in several BRIC/MIST countries as part of a broader move by regulators to address existing drug lag times. Staffing levels at national medicines agencies are being increased, review systems are being fine-tuned, and review target times are being trimmed. Mexico, where regulators now recognize marketing authorizations issued in the US, EU, and several other developed markets, has witnessed the most dramatic improvement in average drug approval times. Significant changes are also afoot in China, although some key measures there appear designed to favor local manufacturers.

- Pricing – While drug prices in the private sector remain free from regulatory control in Mexico and Indonesia, more interventionist approaches are being pursued in most other BRIC/MIST markets, including India. Institutional market prices are under much greater pressure, which is being exerted variously by the imposition of explicit controls and/or more aggressive procurement policies. Major changes will be witnessed in China following a recent overhaul of pricing regulations. These will see patent-expired brands forced to compete directly on price with locally manufactured generics, while patented drug prices will be established through negotiations conducted at national level.

- Reimbursement and formulary access – Gaining access to publicly funded reimbursement schedules remains a critical driver of demand in most BRIC/MIST markets, where patient purchasing power and access to private health cover are both limited. Public sector drug budgets are under growing pressure, however, and accessing major public formularies has become increasingly difficult. The situation has deteriorated most dramatically in Mexico, where only a handful of new drugs have been added to formularies operated by the country’s two major payers during the past two to three years. Where health technology assessment agencies have been established (notably in Brazil and South Korea), cost-effectiveness reviews are being used primarily as a tool with which to deny or severely restrict access to reimbursement for innovative new drugs. Negotiated risk- or cost-sharing deals will help originators to access reimbursement lists more widely, but this will only be achieved by offering considerable discounts.
- Public sector procurement – Pooled purchasing and increasingly aggressive tendering procedures are being used to drive down procurement costs in most BRIC/MIST countries, while institutional purchases in Brazil and Turkey are subject to compulsory discounts. Provincial procurement policies have had a particularly negative impact on prices in China, where originators will hope that prices negotiated for patented brands at the national level will eliminate pressure exerted at provincial and hospital level.

- Distribution – BRIC/MIST distribution markets vary enormously, from Mexico, where the sector is dominated by a handful of large, powerful wholesalers, to countries such as India and China, where highly populated, multi-layered distribution chains prevail. Consolidation is a common theme, however, and restructuring of the pharmaceutical distribution market will continue in most BRIC/MIST countries. It will be hastened in some markets by the imposition of tighter quality regulations and the introduction of drug traceability programs, both of which will drive up distributor costs. Market forces in India have been nullified to date by the All-India Organization of Chemists and Druggists, which has used its considerable muscle to prevent the emergence of large, regional distributors. Its activities have not gone unnoticed by trade regulators, however, and the organization’s influence will be eroded gradually over time, paving the way for the development of larger, more efficient wholesaling groups.

- Prescribing – Physicians in most BRIC/MIST markets have retained a considerable degree of prescribing freedom. This is partly because the availability of government-subsidized drugs has been restricted largely to the public hospital setting, but also reflects the fact that, where they do exist, prescribing regulations have not been enforced effectively. Physicians are under growing scrutiny, however, especially in markets where government-backed reimbursement has been made available more widely. Monitoring and control systems are tightest in South Korea, but efforts to encourage or mandate cost-effective prescribing are also being stepped up in several other BRIC/MIST markets.

- Promotion and marketing – The degree to which manufacturers are able to influence prescribing trends has long been an issue of concern to regulators in most BRIC/MIST markets. The topic has risen swiftly up the policymaking agenda in recent years, however – partly because governments are picking up a larger proportion of the prescribing bill, but also because revelations surrounding unethical activity have made headlines in several countries. This has received most attention in China, where GlaxoSmithKline was found guilty of bribing hospitals and doctors to prescribe its brands, and where the government has embarked on a broad-based anti-corruption drive that has seen the introduction of new rules governing the conduct of both suppliers and providers. Regulations governing promotional activity have also been tightened in several other markets, while in Turkey, sales reps will be the subject of a mandatory certification program that will be enforced fully from 2019.

**Brazil**

**MARKET OVERVIEW**

With annual sales approaching $20bn, Brazil is the second largest of the eight BRIC/MIST pharmaceutical markets (BMI Research, 2016a). It is dominated in volume terms by locally manufactured generics, but originators have made significant headway, not only in the retail and
private hospital sectors, but also in the institutional market, where a specialist pharmaceutical assistance program (CEAF; Componente Especializado da Assistência Farmacêutica) has enabled patients to access a number of innovative new medicines.

Alongside other initiatives designed to improve patient access to medicines, the CEAF program has sharply driven up government drug spending. Budgets for these schemes have been trimmed in the face of a sharp economic downturn, but patients will continue to pursue access to innovative new drugs through the courts, asserting their constitutional right to healthcare provision. Shifting original brands in the self-pay retail market will pose more of a challenge as the economic climate affects patient incomes.

HEALTH POLICY AND THE ECONOMIC/POLITICAL CLIMATE

The economic climate in Brazil has deteriorated rapidly, while a wide-ranging investigation into corruption and money laundering has seen the country descend into political chaos. President Dilma Rousseff was thrown out of office in August 2016 after the Senate voted to impeach her for violating budget laws. Her removal ended a 13-year period of rule by the left-leaning Workers' Party that was characterized by the pursuit of populist social and healthcare policies. Ms Rousseff has been replaced by former vice president Michel Temer, who has signaled his intent to implement tougher policies in a bid to address Brazil’s ailing economy (Washington Post, 2016). President Dilma Rousseff has been suspended from office, and faces an impeachment trial that could end her political career. Recent events could eventually trigger a change of government, ending a 13-year period of rule by the left-leaning Workers’ Party that has been characterized by the pursuit of populist social and healthcare policies. Coupled with an austere economic outlook, this may affect demand for medicines, and more patients may also be forced to trade down from original brands to generics.

MARKET ACCESS ISSUES AND IMPLICATIONS

Policymakers have implemented several measures designed to speed up clinical trial approval and drug registration procedures (Moeller IP Advisors, 2015). Some issues in both of these areas have yet to be resolved, and originators will still often face frustrating delays, but a gradual reduction in the average time taken to register new drugs is anticipated.

The outlook is less positive, however, where IP protection and the pricing and reimbursement of new drugs are concerned. With the economy in growing trouble, funding access to medicines poses a major challenge for the government, while policymakers are keen to ensure that patients purchasing drugs on an out-of-pocket basis have access to the broadest possible selection of affordable options. This means IP issues are unlikely to be addressed, and will ensure that restrictive pricing and public formulary listing policies remain in place.

Originators will struggle to achieve desired launch prices for innovative drugs, while most applications by manufacturers for the inclusion of new products on public formularies will be rejected. Where patented medicines do gain access to the institutional market, most will be subject to mandatory discounts, eroding purchase prices by around 20% (ANVISA, 2016).
With cost still uppermost in the minds of purchasing agencies, the advantages offered by new drugs in terms of efficacy and/or cost-effectiveness will be accorded less weight in the public sector. Those messages will be received more positively in the private sector, which will remain a key early target for new drugs, especially where they have been denied access to public formularies.
<table>
<thead>
<tr>
<th>Factor</th>
<th>Outlook</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intellectual property protection</td>
<td>Originators will continue to face lengthy patent examination backlogs. They will also be forced to contend with the involvement of ANVISA in the patent examination process, and with the continued absence of explicit protection for original data submitted to regulators.</td>
</tr>
<tr>
<td>Clinical trials</td>
<td>Steps have been taken to speed up CTA procedures, but CONEP continues to act as a major bottleneck.</td>
</tr>
<tr>
<td>Registration</td>
<td>A hiring spree and new electronic review/submission procedures will help ANVISA reduce average drug approval times. There is still no explicit fast track approval procedure for innovative new drugs, however, and new generics with the potential to relieve pressure on public health budgets will be the most likely beneficiaries of priority reviews.</td>
</tr>
<tr>
<td>Pricing</td>
<td>New drug launch prices will be subject to restrictive caps. International referencing will ensure that even products awarded category I pricing status will not achieve requested launch prices.</td>
</tr>
<tr>
<td>Reimbursement and formulary access</td>
<td>HTAs undertaken by CONITEC will restrict access for new drugs to public formularies. The agency has approved less than 20% of manufacturer requests for formulary listings since 2011.</td>
</tr>
<tr>
<td>Public sector procurement</td>
<td>The 2016 budget for spending on catastrophic drug coverage (the CEAF scheme) has been cut by 5%. Compulsory discounts will apply to public purchases of most patented drugs. Few multinational applications for technology transfer agreements, which involve commitments to public procurement, will be approved.</td>
</tr>
<tr>
<td>Distribution</td>
<td>Institutional market supply will be disrupted by funding problems. Late payments by cash-strapped purchasing agencies will pose a growing problem in the sector.</td>
</tr>
<tr>
<td>Prescribing</td>
<td>Patient lawsuits will continue to act as a significant driver of filled prescriptions for innovative new drugs.</td>
</tr>
<tr>
<td>Promotion</td>
<td>Penalties for engaging in corrupt promotional practices have been ramped up following the enactment of the Clean Companies Act at the beginning of 2014.</td>
</tr>
</tbody>
</table>
Russia

MARKET OVERVIEW

Imports dominate Russia's $16bn-plus pharmaceutical market, but the government is pursuing increasingly aggressive import substitution policies in a bid to reduce its reliance on foreign products (Scrip, 2015). As well as boosting prospects for domestic manufacturers, these aim to mitigate the impact that volatile currency movements have had on drug spending in recent years by encouraging more foreign companies to invest in local production capabilities.

The climate for originators servicing the Russian market through imports will be challenging, reflecting the impact of import substitution policies and deteriorating economic conditions, which have affected demand for innovative new drugs in the private sector, and which will undermine efforts to broaden access to subsidized medicines.

HEALTH POLICY AND THE ECONOMIC/POLITICAL CLIMATE

The Russian economy has been hit by falling energy prices and the impact of sanctions imposed following its annexation of Crimea in 2014. Russian gross domestic product (GDP) contracted by more than 3.5% in 2015, and is expected to decline further in 2016 (Tanas, 2016). The economic situation has dealt a blow to health policy plans, which envisaged the phased rollout of a national outpatient drug benefits scheme during the second half of this decade. It will also rule out significant expansion of existing subsidy programs, including a catastrophic coverage scheme that funds the provision of drugs used in the treatment of seven serious diseases, and that has been a significant source of demand for some patented medicines.

Russian president Vladimir Putin, who has been in power for 16 years, appears likely to seek re-election once again in 2018 (Babayan, 2016). Assuming that he does run, and is successful, existing healthcare policy directions will be maintained. If economic recovery allows, this will eventually involve the establishment of broader government drug subsidy programs.

MARKET ACCESS ISSUES AND IMPLICATIONS

<table>
<thead>
<tr>
<th>Table 16: Market access outlook in Brazil</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Factor</strong></td>
</tr>
<tr>
<td>ANVISA = National Health Surveillance Agency (Agência Nacional de Vigilância Sanitária); CEAF = specialist pharmaceutical assistance program (Componente Especializado da Assistência Farmacêutica); CONEP = National Commission on Ethics in Research (Comissão Nacional de Ética em Pesquisa); CONITEC = National Committee for Health Technology Incorporation (Comissão Nacional de Incorporação de Tecnologias no Sistema Único de Saúde); CTA = clinical trial application</td>
</tr>
</tbody>
</table>

Source: ANVISA, 2016; Interfarma, 2015; Moeller IP Advisors, 2015; PhRMA, 2016; Scrip, 2013
Drug registration review times will improve, while the Eurasian Economic Union could provide originators with a route through which to obtain regional approvals for new products. This is one of the few bright spots on an otherwise gloomy horizon for foreign companies targeting the Russian market, however.

Orphan drugs have been exempted from the otherwise comprehensive local trial requirements introduced in Russia at the beginning of this decade, but hopes that regulators might issue more widespread waivers appear to have been dashed (Pink Sheet, 2016). The likelihood that Russia will deliver on key IP protection commitments has also receded, while the establishment of more restrictive patentability criteria and compulsory licensing provisions have both been the subject of recent discussion by influential policymakers.

The government has also stepped up its import substitution drive, with pricing and public procurement rules stacked increasingly in favor of domestic manufacturers. This may prompt more foreign companies to strengthen local production capabilities, but current policy trends and the difficult economic climate will act as constraints on the number of innovative new drugs being brought to market in Russia.
Table 17: Market access outlook in Russia

<table>
<thead>
<tr>
<th>Factor</th>
<th>Outlook</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intellectual property protection</td>
<td>The IP protection outlook has deteriorated, and Russia is unlikely to deliver on some key WTO commitments in the near future. Regulators are mulling over the imposition of more restrictive patentability criteria, compulsory licensing has emerged as a potential threat, and early court rulings have failed to uphold data protection claims.</td>
</tr>
<tr>
<td>Clinical trials</td>
<td>Orphan drugs are now exempt from local trial requirements, but proposals to issue more widespread trial waivers have been blocked by the Ministry of Industry and Trade. An abbreviated CTA procedure has been established, but is unlikely to trigger a significant increase in the number of new drugs seeking access to the Russian market.</td>
</tr>
<tr>
<td>Registration</td>
<td>New drug approval timelines have been reduced, while the establishment of harmonized EAEU registration requirements will benefit originators targeting regional introductions.</td>
</tr>
<tr>
<td>Pricing</td>
<td>Price controls will continue to hand local manufacturers a competitive advantage where products on the EDL are concerned.</td>
</tr>
<tr>
<td>Reimbursement and formulary access</td>
<td>Plans for the phased introduction of a national outpatient drug benefits scheme appear to have been put on hold in the face of the economic downturn. Funding considerations will also rule out significant near-term expansion of existing reimbursement schemes.</td>
</tr>
<tr>
<td>Public sector procurement</td>
<td>New procurement rules could freeze foreign suppliers out of the EDL tender market if two or more EAEU-based manufacturers submit bids. Domestic companies will also retain a pricing advantage when bidding for tender business.</td>
</tr>
<tr>
<td>Distribution</td>
<td>The squeeze on distributor margins will drive some further consolidation of the wholesale market. Coupled with moves by some distributors to handle fewer imported drugs, this could pose problems for foreign companies without a local manufacturing presence.</td>
</tr>
<tr>
<td>Prescribing</td>
<td>New rules obliging physicians in the public sector to prescribe by INN have been watered down, and are not being enforced strictly. A tougher approach will no doubt accompany the eventual introduction of a national outpatient drug reimbursement scheme.</td>
</tr>
</tbody>
</table>
India

MARKET OVERVIEW

Still almost exclusively a self-pay market, India poses particular challenges for originators seeking a share of sales worth approximately $17bn (BMI Research, 2016b). Most original brands face competition from a host of locally manufactured generics, while the prices of patented medicines are beyond the pockets of many patients in a country where annual per capita spending on healthcare is less than one-tenth of the OECD average.

Flexible pricing and payment strategies adopted by multinationals have helped to drive sales of some new drugs, and the pendulum should swing gradually in favor of research-based companies as the number of patent-protected products on the market increases. Patented drug prices will be scrutinized closely, however, and may eventually be subjected to explicit controls.

HEALTH POLICY AND THE ECONOMIC/POLITICAL CLIMATE

Indian Prime Minister Narendra Modi made some extravagant health policy pledges in the run-up to the 2014 election that saw his Bharatiya Janata Party secure a landslide victory. He appears unlikely to deliver on his central promise to create a universal health assurance scheme, but recently unveiled a new initiative under which the government will fund a proportion of costs associated with hospitalization. Critics say the initiative will not make a major difference to the plight of many poor patients, but it could, if implemented, help to drive up sales of costly inpatient drugs (The Times of India, 2016).

Partial funding of catastrophic hospital costs has the potential to trigger a significant increase in government healthcare spending, which remains pitifully low at little more than 1% of GDP (WHO, 2016). Nevertheless, it is unlikely to meet the target of 2.5% laid down in the 2015 draft national health policy plan.
MARKET ACCESS ISSUES AND IMPLICATIONS

India will remain among the most challenging BRIC/MIST targets for originators, reflecting the almost complete absence of subsidized pharmaceutical provision, the limited nature of protection offered by the country's IP laws, fierce competition from local generics manufacturers, and an increasingly interventionist approach to drug pricing.

Coupled with IP protection shortcomings, current clinical trial regulations will deter multinationals from pursuing the registration of many new drugs in India until issues surrounding sponsor liability and compensation are ironed out (PhRMA, 2016). Trial waivers will smooth the path to market for orphan drugs and some other innovative products, but country-specific pricing strategies and flexible payment programs will be required to help generate the sale of such products at significant levels.

The catastrophic coverage scheme unveiled by the government at the beginning of 2016 could act as a significant driver of demand for original brands. Multinationals could soon face the introduction of a less positive policy, however, in the shape of patented drug price controls.
Table 18: Market access outlook in India

<table>
<thead>
<tr>
<th>Factor</th>
<th>Outlook</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intellectual property protection</td>
<td>The draft National Intellectual Property Rights Policy approved by the cabinet in May 2016 offers little encouragement for originators. Restrictive patentability criteria and the refusal of second-use patents will continue to frustrate multinationals, which will also struggle to prosecute their IP rights.</td>
</tr>
<tr>
<td>Clinical trials</td>
<td>Efforts will be made to amend new regulations, introduced in 2013, which have triggered a sharp fall in the number of clinical trials being sponsored by manufacturers. Local trial waivers may also be granted more widely in a bid to encourage the launch of more innovative new drugs.</td>
</tr>
<tr>
<td>Registration</td>
<td>Trial waivers and the possible establishment of a fast track approval pathway for orphan drugs are among developments that could expedite the registration process for some innovative new drugs. Manufacturers will continue to resist efforts to cancel registrations for some fixed-dose combination products.</td>
</tr>
<tr>
<td>Pricing</td>
<td>The number of drugs subject to direct pricing control has increased sharply since 2013, affecting many original brands as well as local generics. The establishment by multinationals of flexible pricing strategies and patient access programs for innovative products may not be sufficient to rule out the eventual imposition of direct controls on patented drug prices.</td>
</tr>
<tr>
<td>Reimbursement and formulary access</td>
<td>Low-cost generics dominate subsidized medicines provision where this exists, and patients foot the bill for original brands. A new scheme offering up to $1,500 per family to cover hospitalization expenses could help to drive up demand for originator products.</td>
</tr>
<tr>
<td>Public sector procurement</td>
<td>State and federal tenders will remain of little interest to originators, with purchases limited almost exclusively to low-cost generics.</td>
</tr>
<tr>
<td>Distribution</td>
<td>The AIOCD will continue to act as a barrier to consolidation of the distribution market. The prevailing situation will inflate distribution costs and limit the ability of manufacturers to maintain control over the supply of their brands to end-users.</td>
</tr>
<tr>
<td>Prescribing</td>
<td>The Ministry of Health has drawn up plans for the introduction of mandatory generic prescribing. It remains to be seen whether these will be implemented and, if they are introduced, how effectively they can be policed.</td>
</tr>
</tbody>
</table>
China

MARKET OVERVIEW

Driven by a combination of rapid economic growth and the rollout of new health insurance schemes, pharmaceutical sales in China have risen dramatically over the past decade. Worth approximately $109bn by 2015, China is now the world's second largest pharmaceutical market, and is responsible for almost 54% of the entire BRIC/MIST market total (BMI Research, 2016c).

While market growth has slowed, sales are still rising at double-digit rates (BMI Research, 2016c). Most multinationals are now posting growth at rates below the market average, however, while exchange rate movements have eroded sales reported by originators in China. With a period of more modest overall market growth anticipated in the wake of the latest policy reforms, foreign companies will have to work harder to grow their Chinese businesses through the remainder of this decade. The latest reforms aim to remove the profit motive from hospital prescribing, which is the dominant source of drug sales, while pricing and public procurement reforms will act as additional constraints on market growth rates.

HEALTH POLICY AND THE ECONOMIC/POLITICAL CLIMATE

With basic health insurance coverage rates now in excess of 95%, policymakers have begun to pursue improvements in the quality and efficiency of provision. This will require further substantial investment, and the slowdown in economic growth rates will affect the pace at which future reforms are implemented, especially in the country's less prosperous provinces.

Major goals include strengthening the health infrastructure, harmonizing standards of provision, and expanding the range of subsidized services available to patients. Progress in these areas will drive a further increase in demand for medicines, but efforts to curb drug spending will be stepped up. Pharmaceutical cost-containment measures will affect drug prices, while also encouraging the use of generics rather than original brands where appropriate.

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**Table 18: Market access outlook in India**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Outlook</th>
</tr>
</thead>
<tbody>
<tr>
<td>Promotion</td>
<td>Manufacturers look set to face the introduction of a new, mandatory code of marketing ethics, having failed to comply with a voluntary version introduced at the beginning of 2015.</td>
</tr>
</tbody>
</table>

AIoCD = All-India Organization of Chemists and Druggists; IP = intellectual property

Source: Datamonitor Healthcare; Lexology, 2016; PhRMA, 2016; The Economic Times, 2016; The Times of India, 2015; WHO, 2016
MARKET ACCESS ISSUES AND IMPLICATIONS

Bringing new drugs to market in China looks set to become a quicker and less onerous task for originators. Prices achieved by these products will be subject to stronger downward pressure, however, while generating sales of original brands will become more challenging.

Key recent developments include the relaxation of data requirements in support of patent applications. This has already driven a significant reduction in the number of applications being rejected by the State Intellectual Property Office (MIP, 2015). Regulators have also taken steps to address China’s growing drug lag time. Local clinical trial requirements have been relaxed, access to fast track and priority review procedures has been broadened, and the Chinese Food and Drug Administration has embarked on a major recruitment drive (CIRS, 2015). Originators will call for the clarification of criteria governing access to expedited review pathways, however, with current rules appearing to rule out fast track reviews for drugs that have already been approved or marketed outside China.

Pressure on multinational drug prices will increase following reforms that have seen the abolition of price premiums previously enjoyed by original brands. Under new pricing regulations, patent-expired brands will be forced to compete directly on price with generics. Regulators have also begun to pursue the negotiation of national prices for patented brands (Fierce Pharma, 2016). In theory, these will apply throughout the provinces, ruling out additional negotiations at provincial or hospital level, and manufacturers have agreed to substantial discounts in early national pricing agreements.

Hospital reforms have the potential to drive even bigger changes in the dynamics of the Chinese market. These aim to improve levels of quality and efficiency in the sector, and include measures designed to remove the profit motive from hospital drug purchasing and prescribing. If these are implemented widely they will have a major impact, not only on hospital prescribing volumes, but also on prescription choices in the sector, with generics set to pose a much greater threat to original brands (Fitch, 2015).
### Table 19: Market access outlook in China

<table>
<thead>
<tr>
<th>Factor</th>
<th>Outlook</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intellectual property protection</td>
<td>Patent examination guidelines have been relaxed, allowing for the submission of additional data after initial filings. Linkage issues, weak patent enforcement systems, and limited data protection provisions continue to frustrate originators, however, while new regulations look set to permit the submission and approval of generic registrations while patents are still in force, enabling generic launches immediately following patent expiry.</td>
</tr>
<tr>
<td>Clinical trials</td>
<td>Local trial requirements have been relaxed, enabling the submission of data from local centers participating in multi-country trials. Clinical trial approval procedures have also been overhauled in a bid to expedite CTA timelines.</td>
</tr>
<tr>
<td>Registration</td>
<td>Regulators have implemented or tabled a range of measures designed to address China’s drug lag time. Registration fees have been hiked in a bid to discourage multiple generic submissions, the CFDA has embarked on a hiring drive, and a new drug classification system has been established for registration purposes. Access to expedited review pathways remains limited, however, with only “world-first” drugs appearing to qualify.</td>
</tr>
<tr>
<td>Pricing</td>
<td>The first nationally negotiated prices for patented drugs were announced in May 2016. In theory, these will not be subject to further negotiation at provincial or hospital level. Price premiums on patent-expired brands have been abolished.</td>
</tr>
<tr>
<td>Reimbursement and formulary access</td>
<td>Publication of a new NRDL, which has not been updated since 2009, is expected by the end of 2016. Some provincial lists are significantly more comprehensive than the national version, and obtaining provincial listings for new drugs will remain a priority for originators.</td>
</tr>
<tr>
<td>Public sector procurement</td>
<td>Harmonized approaches to provincial drug procurement are being pursued. New guidelines will have major implications for patent-expired brands, which will be required to compete directly on price with generics for provincial tender contracts.</td>
</tr>
<tr>
<td>Distribution</td>
<td>Competitive pressures and the imposition of tighter quality standards will drive further rapid consolidation of the distribution market.</td>
</tr>
</tbody>
</table>
Mexico

MARKET OVERVIEW

Worth a little over $11bn, the Mexican pharmaceutical market has increased in value at low single-digit rates in recent years, and growth appears unlikely to quicken significantly in the foreseeable future (BMI Research, 2016d). Pricing pressures have been the main constraint on growth rates, reflecting fierce competition for shares of the retail market and the impact of consolidated purchasing on prices in the institutional sector.

Shifting patent-expired brands through retail channels has become increasingly difficult. The sector is dominated by large pharmacy chains, which wield substantial bargaining power, and which have built up extensive ranges of own-label generics that are dispensed on a preferential basis in chain outlets. Accessing major public formularies has also been a struggle for originators bringing new drugs to market, while patented brands have not been entirely immune to pricing pressures imposed by consolidated tendering in the sector.

HEALTH POLICY AND THE ECONOMIC/POLITICAL CLIMATE

Mexico’s economic fortunes are tied closely to those of the US, and GDP growth has been modest over the past three years, averaging between 1.5% and 2.5% (World Bank, 2016). Healthcare spending as a proportion of GDP has increased following the rollout of a basic health insurance scheme for those without employment-based cover (World Bank, 2015). Significant variations in the range and depth of cover available to individual patients persist, however, and a planned merger of existing schemes,
creating a single, harmonized national health insurance (NHI) program, is unlikely to be attempted for several years (JLN, 2015).

MARKET ACCESS ISSUES AND IMPLICATIONS

The time taken by regulators to review applications for the registration of new drugs has fallen sharply since the beginning of this decade. Improvements largely reflect the decision by the Federal Commission for the Protection against Sanitary Risk (COFEPRIS; Comisión Federal para la Protección contra Riesgos Sanitarios) to begin recognizing authorizations granted by regulators in the US and EU (European Commission, 2015). Clinical trial approval procedures have also been overhauled in a bid to cut clinical trial application timelines (BMI Research, 2014).

While the time taken to obtain marketing approvals has declined, originators have found it increasingly difficult to access major public sector formularies, which have a major bearing on the commercial prospects for innovative new drugs. The Social Security Institute (IMSS; Instituto Mexicano del Seguro Social) and its public sector equivalent, the Institute for Social Security and Services for State Workers (ISSSTE; Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado), are both represented on a multi-agency commission that reviews national formulary listings. Both also conduct their own reimbursement reviews, however, and the number of new drugs added to IMSS and ISSSTE reimbursement lists has declined sharply since the beginning of this decade (IMS Health, 2014).

The IMSS has also begun to coordinate bulk tenders for the supply of drugs to a growing range of public purchasing agencies (Mexican Health Review, 2015). This has squeezed procurement prices in the institutional market. Pressure is greatest on multi-source drugs, but substantial savings on patented brands have also been reported by the institute. Prices in the private sector remain free from regulatory control, but competition for shares of the market is fierce, while demand for costly new drugs is limited by the modest size of the population with private health insurance cover.
## Table 20: Market access outlook in Mexico

<table>
<thead>
<tr>
<th>Factor</th>
<th>Outlook</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intellectual property protection</td>
<td>Although Mexico's IP protection framework is relatively strong on paper, patent linkage mechanisms have not been implemented effectively, and weak enforcement mechanisms prevent the timely removal of patent-infringing generics from the market. Data protection is available, but only for data submitted in support of NCEs.</td>
</tr>
<tr>
<td>Clinical trials</td>
<td>New measures designed to cut CTA timelines were introduced in 2014. These aim to cut trial approval times from 90 days to just 30 days.</td>
</tr>
<tr>
<td>Registration</td>
<td>The number of new drugs registered by COFEPRIS has increased sharply since 2011, when the agency began to recognize approvals granted by regulators in the US, EU, and some other highly regulated markets.</td>
</tr>
<tr>
<td>Pricing</td>
<td>Pricing controls in the private sector will remain largely theoretical. Caps on the institutional market prices of patented drugs have been negotiated since 2008, and have generated considerable savings for unilateral purchasing agencies.</td>
</tr>
<tr>
<td>Reimbursement and formulary access</td>
<td>Admission to Mexico’s national formulary does not guarantee that a new drug will be added to reimbursement lists managed by the IMSS and ISSSTE, which are the two most significant public sector payers. Both are plagued by financial problems, and each has pursued an increasingly restrictive approach to new drug listings. Even where listings are eventually approved, reimbursement delays add around two years to the time taken for new drugs to gain full market access.</td>
</tr>
<tr>
<td>Public sector procurement</td>
<td>The IMSS, which began to administer consolidated tenders in 2012, is handling procurement on behalf of a growing number of public sector purchasing agencies. Higher purchasing volumes have driven tender prices down, while tendering rules have been refined in a bid to extract additional savings. The number of states participating in IMSS tenders is expected to increase further.</td>
</tr>
<tr>
<td>Distribution</td>
<td>Competition authorities are looking into the circumstances surrounding a 2015 acquisition in the wholesale sector, and could also investigate allegations that wholesaling giant Nadro and some pharmaceutical companies engaged in price-fixing deals. This could trigger further upheaval in the wholesaling market, which has already undergone considerable restructuring in recent years.</td>
</tr>
</tbody>
</table>
Indonesia

MARKET OVERVIEW

With sales totaling less than $6bn, Indonesia is the smallest of the eight BRIC/MIST pharmaceutical markets (BMI Research, 2016e). It is the world's fourth most populous country, however, and a growing economy, rising incomes, and the rollout of a new universal health insurance scheme all make it a market with considerable long-term potential. The rollout of NHI, which began in 2014, is expected to drive a significant rise in demand for medicines (The Jakarta Post, 2013). Funding constraints mean NHI is being accompanied by the establishment of stronger pharmaceutical cost-containment measures, however, and these will limit rates of increase in market value.

While generics will dominate NHI prescribing, the national formulary (Fornas) includes a number of drugs that are not available in generic form, including more than half a dozen monoclonal antibody-based cancer medicines (IMS Health, 2015). Purchase prices for these products have been negotiated with manufacturers by the Ministry of Health (ISPOR, 2016). While details of pricing negotiations have not been divulged, originators are believed to have offered substantial discounts in return for Fornas listings, which will help to raise the profile of their brands, driving demand in the private sector.

HEALTH POLICY AND THE ECONOMIC/POLITICAL CLIMATE

Indonesia elected a new, reformist president, Joko Widodo, in July 2014. His ambitious economic reform plans aim to drive up growth and reduce the budget deficit, freeing up more funds for investment in infrastructure projects and social programs, including healthcare (CSIS, 2016). Economic growth has continued to follow a gradual downward trajectory since he took office, however, while

Table 20: Market access outlook in Mexico

<table>
<thead>
<tr>
<th>Factor</th>
<th>Outlook</th>
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<tbody>
<tr>
<td>Prescribing</td>
<td>Conditions attached to major public formulary listings will restrict prescribing of innovative new drugs.</td>
</tr>
<tr>
<td>Promotion</td>
<td>Manufacturers will be forced to pursue broader promotional strategies in a bid to counter the impact that pharmacy own-label products have had on sales of third-party brands in the retail market.</td>
</tr>
</tbody>
</table>

COFEPRIS = Federal Commission for the Protection against Sanitary Risk (Comisión Federal para la Protección contra Riesgos Sanitarios); CTA = clinical trial application; IP = intellectual property; IMSS = Social Security Institute (Instituto Mexicano del Seguro Social); ISSSTE = Institute for Social Security and Services for State Workers (Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado), NCE = new chemical entity

Source: Datamonitor Healthcare; BMI Research, 2014; European Commission, 2015; IMS Health, 2014; Mexican Health Review, 2015
the rupiah has fallen sharply in value against the dollar.

GDP growth, which hit a recent peak of 6.4% in 2011, slowed to 4.8% in 2015, and is not expected to climb significantly within the next 1–2 years (BBC, 2016). This will have implications for the country’s new NHI scheme, spending on which has already exceeded expectations, forcing policymakers to hike patient contributions. Providers and suppliers have also complained that initial tariffs and prices set by regulators were too low.

MARKET ACCESS ISSUES AND IMPLICATIONS

In February 2016, the government announced the complete removal of restrictions on foreign ownership of businesses in around 30 industrial sectors (International Business Times, 2016). These included the manufacture of active pharmaceutical ingredients, but, to the disappointment of multinationals, policymakers did not lift existing restrictions on finished drug production, where foreign stakes are capped at 85%.

With poor IP protection deemed by originators to pose a significant risk where the establishment of joint ventures is concerned, their inability to operate independently will continue to act as a constraint on levels of inward investment in the sector. Compulsory licensing also remains a potential threat to originators, while lengthy registration procedures and, in the institutional sector, low prices will also affect levels of activity by multinationals in Indonesia.
### Table 21: Market access outlook in Indonesia

<table>
<thead>
<tr>
<th>Factor</th>
<th>Outlook</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intellectual property protection</td>
<td>Compulsory licenses for generic supply of seven patented HIV and hepatitis B treatments remain in force. While there has been a change of government since existing provisions were renewed in 2012, compulsory licensing of other patented drugs remains a potential threat.</td>
</tr>
<tr>
<td>Clinical trials</td>
<td>With regulators prepared to accept foreign trial data in support of most new drugs, regulatory issues and a chronic shortage of qualified investigators will continue to limit industry-sponsored clinical research activity.</td>
</tr>
<tr>
<td>Registration</td>
<td>Originators must employ the services of a domestic partner to obtain product registrations unless they conduct at least primary packaging activity locally. The registration process also lacks transparency, and applicants often face lengthy delays.</td>
</tr>
<tr>
<td>Pricing</td>
<td>Prices in the private sector look set to remain free from regulatory intervention.</td>
</tr>
<tr>
<td>Reimbursement and formulary access</td>
<td>Access to subsidized medicines under the new NHI scheme is governed by a national formulary (Fornas). The formulary was updated in 2015, and now contains 573 drugs. It is dominated by generics, but does contain a number of patented products. Substantial discounts and risk- or cost-sharing agreements will be required in order to obtain listings for more new drugs.</td>
</tr>
<tr>
<td>Public sector procurement</td>
<td>Tender-based purchasing limits multi-source drug prices in the institutional sector. Purchase prices for single-source products must be negotiated with the Ministry of Health. Risk-sharing agreements have provided the basis for some originator purchases.</td>
</tr>
<tr>
<td>Distribution</td>
<td>Distribution in the institutional market is chaotic, with financial and logistical shortcomings affecting availability of medicines in government facilities.</td>
</tr>
<tr>
<td>Prescribing</td>
<td>A shift towards generic prescribing has been witnessed in public health facilities since the rollout of the new NHI scheme began. Flat-sum hospital payments and weak provider finances will further drive up generic prescribing in the sector in future.</td>
</tr>
</tbody>
</table>
South Korea

MARKET OVERVIEW

Worth just over $15bn, South Korea is by some way the most developed of the eight BRIC/MIST markets (BMI Research, 2016f). As such, while the regulatory framework governing medicines is more advanced, pharmaceutical cost-containment measures are also better established. Indeed, coupled with regular insurance premium hikes, efforts to curb drug spending have been the main tool employed by policymakers in a bid to manage NHI finances. Market growth rates have been limited as a result, and low single-digit increases will remain the order of the day.

While NHI cost-containment measures may have limited overall drug spending, they have not ruled out opportunities for innovative new medicines. Since 2007, around 69% of new drugs seeking access to NHI reimbursement have been included on the positive list. Success rates for oncology medicines and orphan drugs have been lower, but moves to strengthen NHI coverage in these areas should encourage more positive listing decisions in the future (ISPOR, 2014).

HEALTH POLICY AND THE ECONOMIC/POLITICAL CLIMATE

NHI has operated consistently at a surplus since the beginning of this decade. Funding the program will pose a more daunting challenge over the longer term, however, especially if policymakers deliver on commitments to strengthen coverage in key areas such as the treatment of cancer, cardiovascular conditions, and rare diseases. With economic growth falling short of earlier forecasts, policymakers are sure to maintain a conservative approach to NHI budget planning. Having grown by 3.3% in the previous year, the economy slowed in 2015, expanding by a more modest 2.6%. Early predictions of a return to stronger growth in 2016 appear to have been wide of the mark, with the latest central bank forecasts envisaging another year during which GDP will rise by less than 3% (Focus Economics, 2016a).

MARKET ACCESS ISSUES AND IMPLICATIONS

South Korea's IP protection framework has been strengthened in several key areas, while changes to

<table>
<thead>
<tr>
<th>Table 21: Market access outlook in Indonesia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor</td>
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<tr>
<td>---------------------------------------------</td>
</tr>
<tr>
<td>Promotion</td>
</tr>
<tr>
<td></td>
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</tbody>
</table>

KPK = Corruption Eradication Commission (Komisi Pemberantasan Korupsi); NHI = national health insurance

regulations governing clinical research and the drug approval process will favor originators targeting the development and registration of new drugs. Gaining access to the NHI reimbursement list at satisfactory prices will remain a challenge for originators, however.

Data published by the national association representing research-based manufacturers show that, on average, patented drug prices in South Korea are lower than those in most other regional markets, including BRIC/MIST countries such as Indonesia and China (KRPIA, 2014). A larger proportion of applications for the reimbursement of new drugs in areas such as oncology and the treatment of rare diseases may be included on the positive list, but manufacturers will be forced to give significant ground on price in return for access to the list.
### Table 22: Market access outlook in South Korea

<table>
<thead>
<tr>
<th>Factor</th>
<th>Outlook</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intellectual property protection</td>
<td>Explicit patent linkage rules were enforced fully for the first time in 2015. These are designed to encourage early generic filings and patent challenges. Other recent changes to established IP laws have seen the introduction of explicit data protection rules, offering five years of exclusivity for NCEs (three years for other new products), and of PTA periods, under which originators may claim compensation for delays in the patent review process.</td>
</tr>
<tr>
<td>Clinical trials</td>
<td>South Korea will retain its status as an attractive location for clinical research, thanks to an efficient regulatory framework and the creation (with government help) of an extensive clinical trials network.</td>
</tr>
<tr>
<td>Registration</td>
<td>Priority and fast track review procedures are available for orphan drugs and those targeting life-threatening or serious diseases. Since 2015, the submission of a REMS has been a requirement for NCE and orphan drug submissions.</td>
</tr>
<tr>
<td>Pricing</td>
<td>Low launch prices will remain a feature of the South Korean market, while current policies will drive the erosion of post-launch prices.</td>
</tr>
<tr>
<td>Reimbursement and formulary access</td>
<td>Access to the NHI reimbursement list will remain relatively liberal, with the prospect of more listings for oncology, cardiovascular, and rare disease drugs. For products that may otherwise be denied access to the NHI list, risk-sharing agreements will offer a path to reimbursement.</td>
</tr>
<tr>
<td>Public sector procurement</td>
<td>Sales and margins in the institutional sector will both come under pressure following the introduction of the RSDE initiative. The scheme, which was introduced towards the end of 2014, rewards providers for purchasing drugs at lower prices, and for cutting overall drug use.</td>
</tr>
<tr>
<td>Distribution</td>
<td>Rising costs and restrictive pricing policies will drive further consolidation in the pharmaceutical distribution market.</td>
</tr>
<tr>
<td>Prescribing</td>
<td>Original brands will be prescribed more widely for the treatment of conditions in four key disease areas (oncology, cardiovascular disease, cerebrovascular disease, and rare diseases) in which NHI coverage is being strengthened.</td>
</tr>
<tr>
<td>Promotion</td>
<td>Promotional activity will be scrutinized closely as regulators maintain their drive to root out illegal rebating.</td>
</tr>
</tbody>
</table>
Turkey

MARKET OVERVIEW

Demand for medicines in Turkey has increased sharply following the rollout of the country’s NHI scheme, but the imposition of rigorous pharmaceutical cost-containment measures has kept drug spending firmly in check. The partial relaxation of currency-based pricing controls in 2015 has eased some of the pressure that had built up on prices, while rising demand for specialty medicines is fueling growth in the hospital sector (Pharmaceutical Executive, 2015). As a result, market value, which reached $7.6bn in 2015, is expected to increase at a rate of close to 10% in 2016 (BMI Research, 2016g).

The Social Security Institution (SGK; Sosyal Güvenlik Kurumu) now foots approximately three-quarters of the national drug spending bill, and regulators will be determined to keep the lid firmly on pharmaceutical reimbursement costs (Gürsoy, 2016). Coupled with IP protection issues, regulatory delays, and the implementation of policies that favor domestic manufacturers, this will complicate the operating environment faced by originators targeting import-based supply of the Turkish market.

HEALTH POLICY AND THE ECONOMIC/POLITICAL CLIMATE

The Turkish economy grew by 4% in 2015, and while a modest slowdown is anticipated, GDP growth rates are not expected to dip below around 3.5% over the next two years (Focus Economics, 2016b). The country faces considerable social, political, and geopolitical challenges, however, any or all of which could affect future economic stability and growth rates – a fact that was underlined by events in July 2016, when opponents of President Erdogan staged an attempted coup.

Turkey’s healthcare system has also come under growing pressure following the influx of some 2 million Syrian refugees into the country. This will hinder efforts to strengthen coverage offered by the NHI scheme, and will ensure that policymakers continue to pursue a highly cost-conscious approach to healthcare provision. Some cost-containment measures will be implemented on an ad hoc basis, giving stakeholders little time to prepare for changes in the dynamics of the healthcare market in general, and the pharmaceutical market in particular.

MARKET ACCESS ISSUES AND IMPLICATIONS

<table>
<thead>
<tr>
<th>Factor</th>
<th>Outlook</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCE = new chemical entity; NHI = national health insurance; PTA = patent term adjustment; REMS = Risk Evaluation and Mitigation Strategy; RSDE = Rewards for Saving Drug Expenditure</td>
<td></td>
</tr>
</tbody>
</table>

Source: Datamonitor Healthcare; APAC, 2015; Kasan Insight, 2015; Lex Mundi, 2016; PhRMA, 2016; WHOCC, 2014
Although the regulatory framework governing pharmaceuticals has been aligned broadly with EU norms, significant differences remain. Some of these reflect the content of regulations, but others are the result of divergent approaches to the interpretation of key rules. This has posed problems for originators in a number of areas, including IP protection and the drug approval process.

Good manufacturing practice inspection requirements will continue to inflate average approval times for new drugs, while pricing and reimbursement issues will continue to hinder market access (Gür Ali, 2013). Current rules will dissuade originators from pursuing reimbursement listings for some new drugs, which will be supplied instead on an ad hoc basis. Risk- or cost-sharing agreements will provide a route to reimbursement listing for some new drugs that may otherwise be denied access to the SGK schedule (Scrip, 2016b).
<table>
<thead>
<tr>
<th>Factor</th>
<th>Outlook</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intellectual property protection</td>
<td>The validity of second-use patents was confirmed by the Supreme Court in 2015, while a revised draft of regulations designed to bring other IP provisions into line with the European Patent Convention was released by the Turkish Patent Institute in February 2016. Weak patent enforcement mechanisms and ineffective data protection are among outstanding issues affecting originators in Turkey.</td>
</tr>
<tr>
<td>Clinical trials</td>
<td>New regulations that took effect in 2013 are designed to reduce clinical trial approval times. The rules allow for the simultaneous submission of protocols at local and national level, and also enable protocol reviews by external ethics committees.</td>
</tr>
<tr>
<td>Registration</td>
<td>GMP certification requirements continue to delay new drug approvals. More inspectors have been hired, while GMP audits for innovative or life-saving products are being prioritized, but this could see new drugs that do not qualify for priority inspections exposed to even lengthier delays.</td>
</tr>
<tr>
<td>Pricing</td>
<td>A new mechanism for calculating and updating exchange rates used to set drug prices was introduced in July 2015. International referencing and the imposition of mandatory discounts on institutional purchases will continue to limit prices, however.</td>
</tr>
<tr>
<td>Reimbursement and formulary access</td>
<td>A government action plan published in December 2015 calls for preferential reimbursement of locally manufactured drugs and, where appropriate, delisting of imported products from the national reimbursement list. Price-volume agreements, which were struck with the manufacturers of novel hepatitis C drugs in 2016, could pave the way for the reimbursement of more new drugs in future.</td>
</tr>
<tr>
<td>Public sector procurement</td>
<td>Mandatory discounts are imposed on products sold into the institutional market, while moves towards pooled hospital purchasing have begun. The first city-level hospital tenders were issued in 2014, and have already driven procurement prices down.</td>
</tr>
<tr>
<td>Distribution</td>
<td>New good distribution practice standards are scheduled for implementation in 2016. Coupled with the impact of falling prices on wholesaler margins, costs associated with good distribution practice compliance will drive further consolidation within the distribution market.</td>
</tr>
</tbody>
</table>
Table 23: Market access outlook in Turkey

<table>
<thead>
<tr>
<th>Factor</th>
<th>Outlook</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prescribing</td>
<td>A new “rational drug use” action plan unveiled in 2014 will involve the introduction of new clinical guidelines, decision support systems, and prescription monitoring initiatives. Financial incentives for cost-effective prescribing may eventually be introduced as part of this scheme.</td>
</tr>
<tr>
<td>Promotion</td>
<td>Stricter limits on promotional activity have been imposed by regulations implemented in 2012 and 2013. A new sales rep certification scheme has also been established, with full compliance required by 2019.</td>
</tr>
</tbody>
</table>

GMP = good manufacturing practice

Source: Datamonitor Healthcare; Erciyas and Karakulak, 2015; Gür Ali, 2013; Mene et al., 2013; Scrip, 2016b

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APPENDIX

About the author

Tim Wesley is a writer, editor, and analyst with 30 years of experience in the healthcare sector. Previously employed as an editor and, latterly, managing editor at PJB Publications (now part of Informa), he has worked on a freelance basis for the past 20 years, executing commissions for a range of clients that includes market research specialists, multinational healthcare corporations, regional and global industry associations, and national newspapers.

Scope

This report provides an in-depth review of recent developments affecting the market access climate in each of the eight BRIC/MIST countries (Brazil, Russia, India, China, Mexico, Indonesia, South Korea, and Turkey). It is structured primarily along product lifecycle lines, addressing access issues at all stages, from filing for and securing intellectual property protection, through product development, registration, pricing, and reimbursement to distribution, promotion, and marketing. Characteristics and trends common to the eight BRIC/MIST markets are outlined in an introductory section, while the study is completed by a series of country-specific profiles, drawing together key developments that will affect access to each of the eight markets through the remainder of this decade.

Where appropriate, regulatory systems and procedures are outlined to set key developments in context, but the report is not intended as a guide to regulatory frameworks or systems. Its focus is also firmly fixed on the institutional and, where appropriate, self-pay retail sectors, which dominate emerging markets, and within which market access issues are most complex.

Methodology

Information on significant developments with implications for market access in each of the eight BRIC/MIST markets was obtained from a broad range of sources, including Informa’s proprietary publications, national health ministries and regulatory agencies, national and international industry associations, journals, other specialist healthcare publications, and national and global media organizations.