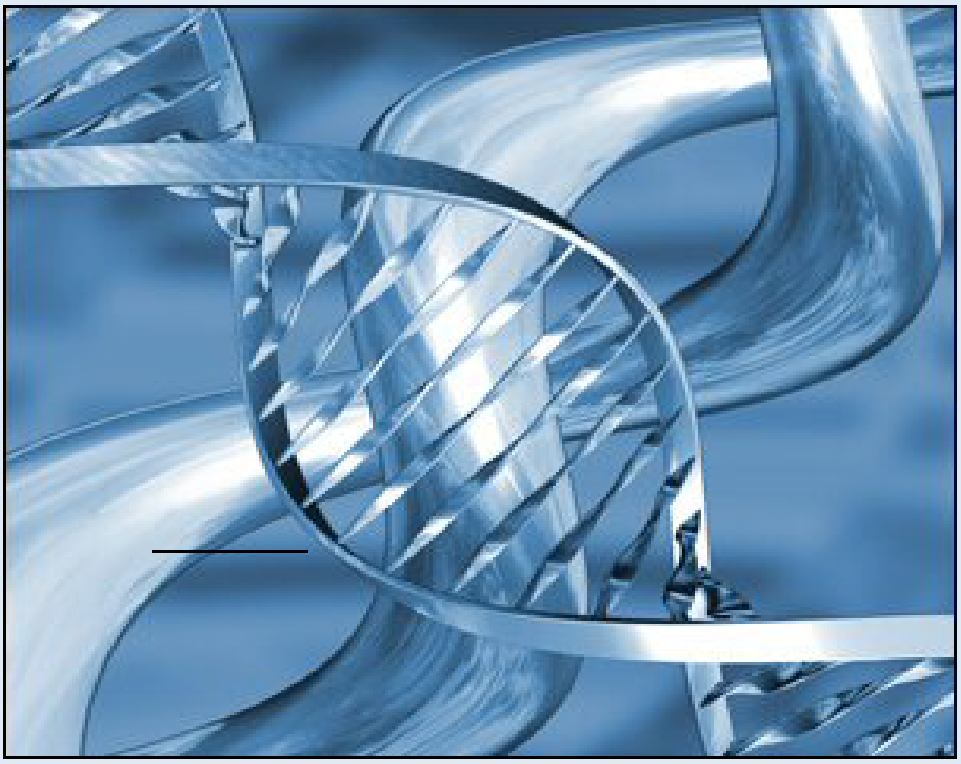
Veracity Health

Synopsis

October 2009



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Key Opinion Leader Interview - Professor Timo Vesikari

Novel Technologies Are Expanding Drug Delivery using Dermal Patches

Welcome to the very first edition of Veracity Health's in-house publication, *Synopsis*. In this regular review, we will be presenting biotech, pharma and medical device topics which are of immediate interest due to research developments, recent market events or strategic opportunities. On occasion, *Synopsis* will also contain interviews with industry leaders and well-known scientific researchers.

In this issue, we look at three subjects and report one interview.

The BRIC (Brazil, Russia, India, China) pharma, biotech and medical device markets are moving to center stage in many companies' marketing strategies, as the established markets' sales growth rates slow to around 5%. In the first of a series of articles focusing on BRIC, the article in this edition of *Synopsis* lays the foundation by giving a review of the healthcare situations in each country, with analysis of various market segments which we forecast will experience strong growth in the coming years.

Our second article focuses on transdermal drug delivery systems (TDS). TDS technology has pushed into the spotlight recently with intriguing developments that for some treatments may make the hypodermic needle a thing of the past. Patch technology has been around for some twenty years, but only recently have some companies figured out ways to move larger molecules across the skin barrier. We map the competitive landscape in this area and outline developments which are likely to drive attractive sales numbers over the next several years.

With the tremendous worldwide effort to combat the A/H1N1 pandemic, the US finally appears to be joining the European Union in considering increased usage of adjuvants in vaccines. The article in this edition looks at adjuvants and vaccines in development and what companies are poised to fill the US thirst for novel adjuvants.

We have had the distinct pleasure of conducting an interview with Prof. Timo Vesikari, a world authority on vaccines, who spoke with us about what he considers to be the infectious disease areas in greatest need of efficacious vaccines. He also provides comment upon governments' current states of readiness; if H1N1 (relatively mild to date) were to suddenly cause increased rates of mortality, or if avian influenza (H5N1) changed in such a way that it crossed easily from animals to humans, would we now be prepared?

We at Veracity Health hope that you enjoy this first edition. If you would like to be on our mailing list to receive *Synopsis*, please send us an email. We would certainly appreciate hearing your comments and suggestions for future articles and improvements. Please send these to info@veracityhealth.com.

The BRIC Economies - A Backgrounder to Pharma and Medical Device Opportunities

In 2007 the BRIC countries' share of global GDP amounted to almost 13% (measured at market exchange rates) or to 20% (in Purchasing Power Parity terms), indicating the importance of these markets within the global economy.

In this issue of the Veracity Health newsletter we begin with the first in a series of articles highlighting the market opportunities within the pharmaceutical, biotechnology and medical device sectors in the emerging BRIC economies (Brazil, Russia, India and China). With the first of the articles presented here we commence with a general overview of the healthcare structures within these countries and concentrate upon an analysis of a few key medical device markets within China and India. In follow-on articles we look more closely at the medical device and pharma industries in Brazil and Russia but we will also return to look at different markets in China and India.

In spite of the economic slowdown the BRIC economies remain in relatively good shape

In 2008 despite the global downturn, the BRIC economies generally bucked the trend of contracting growth rates. The BRICs, with 40% of the world's population spread out over three continents, already account for nearly a quarter of global GDP. A report by the IMF in June 2009 noted that despite a forecast contraction in growth of the Russian economy in 2009 (in part because Russia has suffered greater fallout from plunging commodity prices than many other countries) and the fact that Brazil's economy is undergoing consolidation, the BRICs enjoy greater potential for stability and recovery.

With respect to China in particular the adverse economic conditions have prompted a surge in investment in the country's infrastructure rather than a defensive policy of cost cutting. The healthcare sector has been one area which is benefiting from China's reform plans. Over the last few years each of the BRIC nations have put in place a number of initiatives aimed at improving their expenditure on health and access of poorer sections of their societies to health services. The governments in these countries also, by way of their actions, seem to recognize that continued economic growth will come on the back of investment in infrastructure and their abilities to foster and nurture technological innovation.

Table 1 - Demographic, economic and healthcare parameters for Brazil, Russia, India and China

Parameters (2008 estimates)	Brazil	Russia	India	China
Population (millions)	192	142	1148	1329
% of population aged 65 or above	6.3	14.1	5.2	8.0
GDP ($bns)	1,575.2	1,671.5	1,160.4	4,195.9
Total expenditure on health ($bns)	132.3	86.9	58.0	197.2
Total expenditure on health (%of GDP)	8.4	5.2	5.0	4.7
Total expenditure on health (per capita)	690	613	50	148

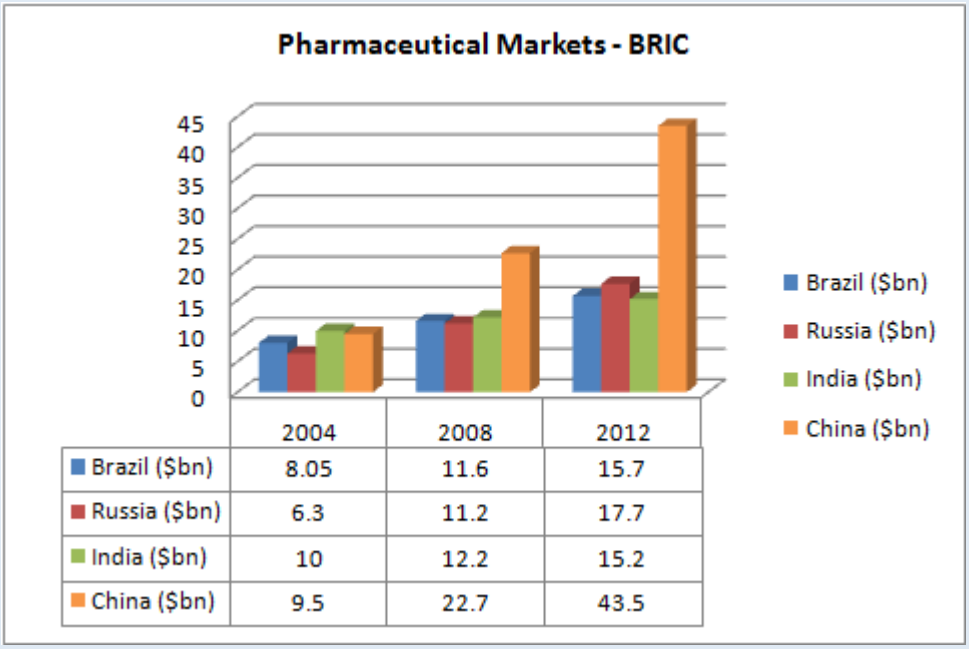
Source: KPMG, EIU data

Pharmaceutical Market developments

The expansion of the global pharmaceutical markets has slowed in many of the traditional powerhouses or engines of growth. Year on year increases in sales in the largest of the global markets, the USA, has slowed considerably; the prescription drug market there registered a positive uptick of only 1.3% in 2008 to $291bn, according to the company IMS. For 2009 IMS predicts that the US pharmaceutical market is projected to contract 1-2%, representing a historic low.

By contrast, double digit market growth has been experienced in the BRIC countries in the last few years and this trend is set to continue. It is expected to do so to such an extent that these countries are being seen as providing the necessary momentum to drive the future businesses of the major multinational pharma manufacturers.

Chart 1 - Pharmaceutical Markets in the BRIC countries, 2004-2012



	2004	2008	2012
Brazil ($bn)	8.05	11.6	15.7
Russia ($bn)	6.3	11.2	17.7
India ($bn)	10	12.2	15.2
China ($bn)	9.5	22.7	43.5

Sources: Company Reports/Financials, Industry reports, internal data sourced and analysed at Veracity Health.

A Veracity Health analysis forecasts that by 2012 the combined revenues of the BRIC pharma markets will reach $96.1bn from a value of $59bn in 2008, demonstrating a 2008-2012 CAGR of 13%.

Market Trends - Pharmaceutical/Biotech

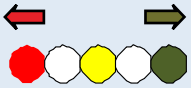
Drivers

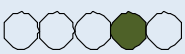
The federal government in Brazil has created a special financing programme with the intention of enticing domestic pharma manufacturers to increase R&D, increase the level of local production of medicines and foster an environment in which M&A activity can thrive.

Russian government is encouraging domestic pharma companies to increase investment in R&D, commercialise innovative drug candidates and ultimately challenge dominance of foreign drug imports.

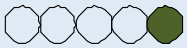
Key:

Strength of Restraint **Strength of Driver**

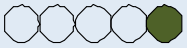




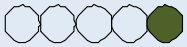
The market leding Russian pharma manufacturer Pharmstandard entered into a JV with the company Lekko to form Generium. Generium will have both research and manufacturing capabilities. The total investment in Generium is approx. $56m. It will specialise in the production of drugs for the treatment of haemophilia, tuberculosis, multiple sclerosis, cancer, and growth hormone deficiency and is expected to have sales of about $200m by 2013.



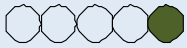
Relaxation of the rules on foreign ownership and a favourable tax regime in India. Goldman Sachs estimates that the cost of setting up and running a new manufacturing facility in India is one-fifth of doing so in other developed countries.



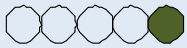
Indian biotechnology sector comprises over 325 companies generating revenues of over US$ 2 billion, estimated to reach US$ 5 billion by 2010.



The Indian pharmaceutical sector, already an emerging global force has 85 FDA approved active pharmaceutical ingredients (API) and formulation manufacturing sites in the country (the highest number outside the US.

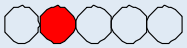


Large pool of talented scientists. Reversal of brain drain of top Chinese and Indian scientists from the USA has been noted. These experts are returning to India and China and are actively involved in setting up specialty pharma, biotech and CROs.

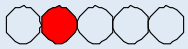


Increasing adherence to IP protection legislation and development of State regulatory authorities will drive pharma/biotech industries.

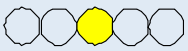
Restraints



The CRMM in Brazil which regulates drug prices has restored price freezes and imposed price controls which will continue to have an impact by decreasing profits for foreign companies.



Drug counterfeiting remains a problem, especially in China, India and Russia.



Growth of the industry will suffer if reforms aimed at widening healthcare insurance coverage is not followed through

Lack of space does not allow us to comprehensively cover the pharmaceutical markets in the BRIC countries and especially not in Brazil and Russia.

In future issues of Synopsis we will provide more detailed analyses of sub segments of the pharma and biotech markets of all these countries either individually or as a group.

Health reforms targeting modernization and enhanced patient access

BRAZIL

Of the four BRIC countries Brazil has the most advanced and best organized healthcare system, but not necessarily the most efficient. It is fair to state that the Brazilian healthcare model has the most comprehensive coverage of the four BRIC nations: anybody can seek medical assistance in any of the hospitals of the national healthcare network.

Many hospitals in Brazil however are poorly located and are considered too small to either operate efficiently or ensure quality. This is problematic given the fact that Brazilians are accustomed to going directly to hospitals when they have a healthcare issue, bypassing assistance at the primary health level. About 60% of Brazilian hospitals have fewer than 50 beds and, to compound matters, are severely underutilized. This inefficient use of resources may, as mentioned, be due to difficulties in getting to the locations coupled with a limited demand for their services. International studies suggest an optimal size of between 150 and 250 beds for hospitals. Despite low efficiency and utilization, many small hospitals survive through subsidies from state and municipal governments.

Economic uncertainty and a resultant cautious attitude meant that in January 2009 the Brazilian government announced a $16bn freeze in overall budget. However, the government stressed that this would not affect the spending already allocated for healthcare and other welfare programs despite the fact that the country has cut healthcare allocations in the past, even in growth years. This was the case in 2007, when the government cut $2.56bn from its healthcare allocation and then only released less than half that amount ($1.02bn) during the fiscal year. The current economic conditions may force the government to make cuts in its healthcare expenditure, which will further delay plans for modernization of the SUS system and could also hinder private insurance uptake in the country. If these scenarios play out, the development of the Brazilian pharma and medical device markets is likely to lag behind what is forecast for China and India in these industry sectors.

Parameters	Brazil
Health System/Infrastructure	Brazil has one of the more advanced healthcare systems among the high-growth economies. It is a two-tier system with a mix of private and public providers and payers. A single public healthcare system – the Sistema Unico de Saude (SUS) – was introduced in 1988. The SUS is financed by both federal and local taxes and has evolved new regulations and services targeting programs for occupational health, women's health, geriatric care, dental care, and care for the increasingly prevalent STD and HIV infections.
Public vs. Private Healthcare	Seventy six percent of the country's population depends on the SUS, the public healthcare system,. Public provision accounted for approximately 45% of healthcare spending in 2006. In 2007, about 40 million people (25% of the population) were covered by private insurance. In 2007 Brazil had 4436 private hospitals and 2719 public hospitals Average size of hospitals is small, approximately 70 beds per hospital

Parameters	Brazil
Healthcare Reforms/Initiatives **2008**	Creation of a new financial transaction tax, Contribuição Social para a Saúde, CSS (Social Contribution for Health) to replace the Contribuição Provisória sobre Movimentação Financeira (CPMF), used to finance healthcare spending. The CSS is a 0.1 percent permanent levy on most financial transactions and is expected to raise $7.2bn. – Proposed new regulations introduced by the Agência Nacional de Saúde Complementar (ANS), the Brazilian health insurance regulator, are expected to improve health insurance provision by encouraging healthy competition amongst the private health insurance providers. The regulations also aim to reduce the waiting period for patients. – Targeting modernization of the public healthcare sector. The Brazilian government is introducing plans aiming for greater focus on prevention, HIV/AIDS education and the improvement of maternity and infant care services.

RUSSIA

In 2006 Russia introduced a number of measures aimed at improving medical care. Healthcare was granted the status of a “national project” to be supervised by then First Deputy Prime Minister Dmitry Medvedev. This resulted in some improvement in the quality of state-provided medical care, especially in terms of equipment upgrades and purchases for state-owned polyclinics and hospitals (in the form of new X-ray, ultrasound, laboratory and endoscopic equipment),

Parameters	Russia
Health System/Infrastructure	6,800 hospitals in 2007 with 1.522m beds. Statistics from that year show that apart from hospitals 18,300 medical institutions were providing out-patient services to the population. Poor infrastructure of Russian hospitals both in terms of buildings and equipment. Approximately 15% of Russian hospitals were built in or before the 1940s and continue to lack basic facilities. The quality of medical services remains relatively low and it is widely accepted that the system is plagued by poor management, understaffing and inadequate equipment at hospitals. The system also needs to be cleansed of inherent corruption which hinders allocation and thus spending in areas where there is greatest need, especially as healthcare spend does not adequately filter down to medium sized and smaller hospitals. Russian healthcare system is represented by three types of healthcare institutions: private, municipal and federal clinics. Article 41 of the Constitution of the Russian Federation guarantees free healthcare services for all Russian citizens. However: there is no “free” healthcare in Russia, the system is based on insurance principles. In practice Russian patients have to pay a lot both to get access to some services or medicines and to get treatment in time. Only 5.2% of GDP is assigned for healthcare (compared against OECD average 8.9% in 2007)
Public vs. Private Healthcare	Private health insurance is taken out by an estimated 5% of the population, the rich elite. In total perhaps 15% of those living in Russia access private healthcare as employees of major corporations. Payment for private health insurance premiums remains out of reach for the majority (85%) of the Russian people. Recent studies suggest that those opting in to private schemes do so mainly in wealthier urban communities rather than in rural areas. Uptake of private medical services increased 18-20% in 2007. Forecasts are for a continuing opt-in for such services at a rate of 12-15% per year.

Parameters	Russia
Healthcare Reforms/Initiatives **2008**	Highest profile health initiative has been the nearly $20bn spent on health care as one of four "National Projects" from 2006 through 2008. Implementation of these programs has, according to the government, raised salaries for family doctors, bought thousands of new ambulances, allocated capital to the construction of 15 new high-tech medical centers, immunized 60 million children, renovated or purchased equipment for hospitals and clinics, and put several thousand HIV/AIDS patients on life-saving medication (see text) Russian Security Council announced two major plans for implementation up until 2020. Health 2020 and Pharma 2020 Health 2020 – aims to provide medical insurance to Russia's entire population and help to increase life expectancy Pharma 2020 – aims to support the R&D and manufacturing activities of domestic pharmaceutical companies in order to simultaneously stimulate local innovation and increase the market share of their domestically produced generic drugs. Industry observers anticipate pricing pressure on multinational pharmaceutical companies will further benefit market penetration by the smaller Russian pharma manufacturers.

reduction in waiting times for various procedures and increased physician salaries.

Government actively encouraging domestic (generic) pharmaceutical manufacturers to invest in R&D and produce innovative medicines

Over the last 3 to 4 years prior to an anticipated slowdown in growth in 2009, the Russian pharmaceutical market has also benefited from the country's economic and political stability. Since no universal coverage for drugs exists in Russia, over 70% of spending on pharmaceuticals is out-of-pocket. The continuing emergence of a growing middle class with disposable income is an important driver of this cash-based retail market.

For those less affluent sections of Russian society a State drug reimbursement scheme, the DLO (Dopolnitel'- noe Lekarstvennoe Obespechenie , or the Provision of Supplemental Medicines), was introduced in January 2005 with the clear purpose of guaranteeing access to medicines at subsidized rates for around 5 million people comprising war veterans, pensioners and low income families. The scheme ran into crisis in 2006 as a result of a corruption scandal which saw funding for the program affected to such an extent that it came close to being abandoned. After the corruption scandal the DLO program was restructured in 2007. In its current form the federal scheme has more than 2000 drugs on an approved list.

Healthcare provision in rural areas remains of a poor quality

While some progress may be made with improved access to drugs, the availability of high levels of medical care overall, especially in rural regions, remains low. Many patients bear at least part of the cost of drugs as well as treatment through making direct payments to physicians or nurses. The regularity and acceptance of such practices leads seasoned observers of the development of the healthcare sector in Russia to harbour the belief that corruption is rife, to the extent that up to 35% of money allocated for health care use is siphoned off. Consequently the necessary investment in services is not filtering down to medium and smaller hospitals.

$4.3bn of federal budget allocated to construction of centres of excellence in cardiology, orthopaedics and neurosurgery

In 2007, in the national 'Health' project, top medical technologies were given a new priority.

Over 130 billion roubles ($4.3bn) of the federal budget were allocated to construct 15 hi-tech medical centers in Russian regions. The choice of location of the centers has been based upon population healthcare needs as well as the presence in the localities of variously qualified personnel.

As a result of selection criteria, cardiovascular surgery has been sited in Penza, Astrakhan, Khabarovsk, Krasnoyarsk and Kaliningrad; traumatology and orthopedics in Cheboksary and Krasnodar, and neurosurgery in Tyumen.

Federal high tech medical centers for Russia – an overview of the project:

The first seven hospitals:
When Vladimir Putin opened the Penza Centre in January 2008, he made interesting comments on the need to assist domestic companies in their development of production facilities to manufacture high quality medicines and medical equipment. Putin pointed out that there were only a few factories producing medical instruments in the country – MIZ-Vorsma and Tumbotino in the Nizhny Novgorod region and the KMIZ factory in Kazan were mentioned. Putin also pointed out that a considerable challenge to the indigenous device industry came from the large volume of imports from China and Pakistan, not all of them conforming to international standards and in some respects of inferior quality compared to Russian built systems.

Table 2 - Russian Hi-Tech Medical centers

	Cardiovascular Surgery	Trauma/ Orthopaedics	Neurosurgery	Others
Locations of first 7 high-tech centers	Khabarovsk Krasnoyarsk Astrakhan Penza	Cheboksary Krasnodar	Tyumen	A children's onco-hematology center is being built in Moscow
Notes	The new equipment purchased for the cardiosurgery hospital in Penza, opened in December 2007, comprised 185 beds, including 40 intensive care beds 1 MRI 1 CT 2 angiography rooms 3 operating theatres			
Locations of on-going builds	Kaliningrad Perm Chelyabinsk	Barnaul Vladivostok Smolensk	Novosibirsk	

Vladimir Putin highlights need to invest in nanotechnology solutions for medicine

Nanotechnology is one area where Putin saw considerable promise and which is likely to see some form of State funding; he felt the use of nanotechnology in medicine should be made a priority. To quote Putin, "the range of its applications is extremely wide, from diagnosis and treatment to the global control of infections, and we need to ensure its practical application."

Low oil prices could impact government spending plans and ongoing healthcare Reform

The Russian government's initiatives with respect to reform and investment in the healthcare sector are well intended. Economic pressures have the capacity to stall Government reform plans, however. In a natural resource-intensive country such as Russia, the falling oil prices and sluggish production of this most valued commodity have impacted government finances dependent precisely on oil and gas taxes for half of its budget revenues. To date, Russia has not announced any cuts in its healthcare spending, but renowned financial services firms such as KPMG feel that the government may cut the previously approved 2009 fiscal spend by US$52bn, or 21%, and reallocate more money to anti-crisis measures in the upcoming budget. Such uncertainties raise questions about Russia's ability to implement its recently proposed healthcare reforms. Regardless of that, its increasingly prosperous citizens are likely to become strong advocates of private health care in the coming decade. If this becomes the case, Russians will come to expect access to the best pharmaceuticals and medical device equipment, boding well for the companies operating in these sectors.

INDIA

The conditions for exporting medical devices to India have significantly improved since the economic reforms of the mid-1990s - import license requirements have been cancelled, majority-owned subsidiaries are possible, and dividends can be paid out abroad.

Some other measures, driving the market are:

Reduction of import and customs duties are incentives designed to drive the medical devices markets in India

- Favorable government policies such as reduction of import duties on medical equipment from 25% to 5%;
- Depreciation limit on medical equipment rose to 40% from 25%, to encourage imports;
- Customs duty on certain types of medical equipment, including X-ray, has been reduced to 5%.
- The Health Ministry has mooted a proposal to set up a series of 'Medical Parks' all over the country to enable domestic health industry to manufacture health equipment in larger volumes. The first of these was opened in Sriperumbudur in May 2008.

Private health insurance, and thus access to private healthcare expected to rise with growing affluence of the Indian middle classes

The primary driver behind the growth of the private health sector in India is the dearth of adequate infrastructure in the public sector. Additionally the private health care providers are relatively better attuned to the requirements of the patients: in order to market their services to prospective patients, they have had to assess the needs of the populations within their "catchment areas." Their services also are geared towards taking advantage of the burgeoning

Parameters	India
Health System/Infrastructure	Development remains primarily urban-centric and does not tackle the pressing needs of rural India. Key statistics regarding infrastructure: Three-tiered healthcare infrastructure, the very bedrock of the public healthcare delivery system, consists of 23,000 PHCs (Public Health Centers), 137,000 Sub Centers and 3000 CHCs (Community Health Centers) Total number of hospitals is 15,097 with 870,161 beds The number of doctors in India is 503,900 There are 737,000 nurses 350,000 pharmacists Medical colleges 162, pharmacy colleges 143
Public vs. Private Healthcare	Private medical services form the larger part of healthcare provision: 70% of the hospitals are private and provide close to 60% of all out-patient care and 40% of in-patient care. Health insurance: less than 10% of the population is covered by health insurance, although there was 44% growth in health insurance during 2006-2007. The medical insurance premium income is expected to grow to $3.8bn by 2012.
Healthcare Reforms/Initiatives	
2005	The National Rural Health Mission (NRHM), a seven-year program targeted at improving healthcare in rural areas by increasing access to comprehensive primary healthcare and strengthening the rural public health infrastructure.
2006	The National Pharmaceutical Policy focused on: • Improving the availability of quality medicines and enhancing the accessibility of essential medicines. • Providing incentives for pharmaceutical R&D and production, to both local and external players. • Mandating price negotiations for patented drugs introduced after January 2005. • Promoting generic drugs.
2007	The government lowered the minimum capital requirement for standalone health insurance companies from $24.1 million to $12 million, providing a further impetus to the health insurance industry.
2008	In the 2008 budget, the government increased its healthcare spending by up to 15%. As part of the reforms, the government offered a five-year tax holiday for hospital construction in Tier-2 and Tier-3 cities to make better treatment available in rural areas.
2009	In its interim budget for fiscal 2009 –10, announced in February 2009, the Indian government cut the total healthcare allocation to $3.13bn, a decrease of 5.76% over the previous year.

In order to address the inadequacies in the public health system, notably the wide gap between rural and urban healthcare infrastructure and low health insurance coverage for the masses, the Indian government has introduced several initiatives. In 2004, under its Common Minimum Program, the government launched a number of schemes aimed at raising public healthcare spending by at least 2 – 3% of GDP.

Increasing investment targeting programmes to strengthen healthcare service provision in rural India

Furthermore, as part of its healthcare agenda, the government has also been increasing the budgetary allocation for its rural healthcare mission, which accounted for $2.75bn out of the total $3.77bn allocated for healthcare in 2008. initiatives have involved a steadily increasing budget allocation for health and family welfare over the past few years. Notably this has risen by 22% in 2006, 22% in 2007 and 15% in 2008.

Analysis of select medical device markets - India

It is not possible to provide a complete overview of the medical devices markets in India and China within the confines of this publication. We have decided therefore to focus attention to the diagnostics/monitoring sectors of the medical device industry, notably looking at ultrasound systems, patient monitoring systems and in vitro diagnostics. One reason for focusing on these sectors is the forecast above average growth rates seen in them and the growing opportunities noted for domestic manufacturers.

Ultrasound - India

The quality and functionality of low end color Doppler systems means that grayscale systems will gradually see declining sales and thus erosion of market share. Price stabilisation is evident in the market driving purchase of systems especially for use in Ob/Gyn and vascular imaging.

Ultrasound - Competitive Landscape

Global multinationals dominant in the Indian ultrasound market

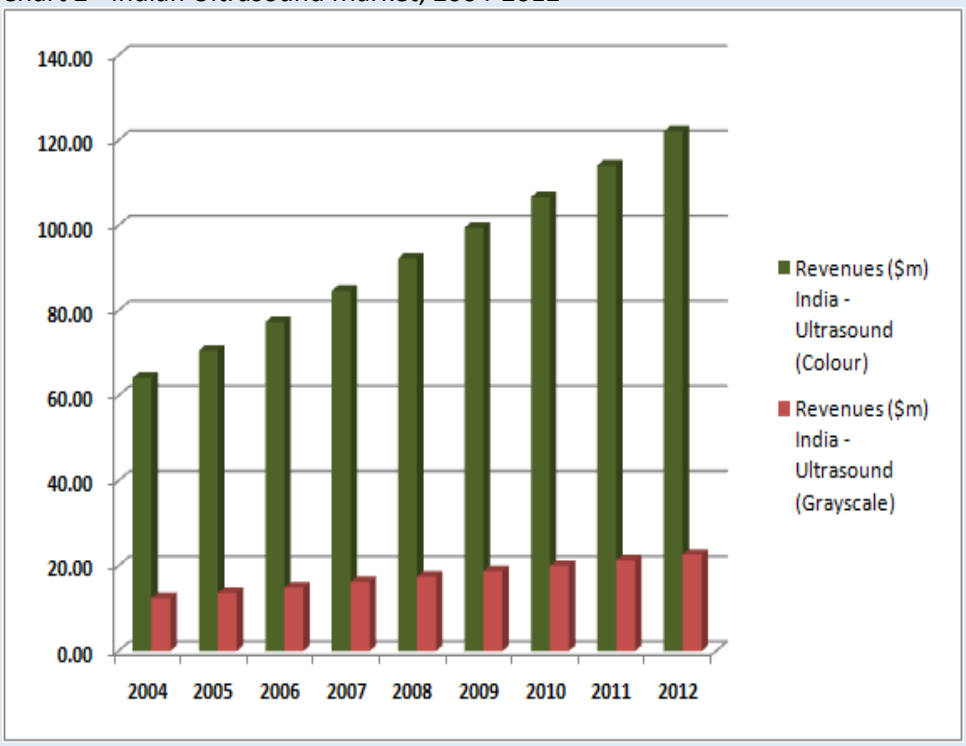
GE Healthcare, Phillips, Siemens, L&T Medical, Aloka (through Trivitron), Toshiba (through Erbis), Esaote. Mindray. Meditronics, SonoSite, Medison (JDS Medison), Shimadzu. Hitachi (through BlueStar)

Ultrasound (Colour) Market CAGR (2004-2012) 8.4%

Ultrasound (Grayscale) Market CAGR (2004-2012) 7.8%

Chart 2 - Indian Ultrasound Market, 2004-2012

Color ultrasound will erode market share of grayscale systems.



Source: Veracity Health analysis

Lack of uniformity of reimbursement for patient monitoring devices acts as restraint on market growth

Patient Monitoring Devices - India

Growth of bedside and telemetry monitoring is driving the Indian market and given the shortage of qualified healthcare personnel the ability to utilize these systems to provide centralized management of patients is important for positive market development. Trends toward home healthcare and remote patient monitoring are considered future key drivers of the market.

Complex return on investment for high-end solutions remains a significant market restraint, limiting demand. Although hospitals are reimbursed for tests, medical procedures, and hospital stays, the reimbursement amount varies according to the number of parameters monitored during the hospital stay. Coupled with the budget restraints effect, this challenge could noticeably dampen the central station market.

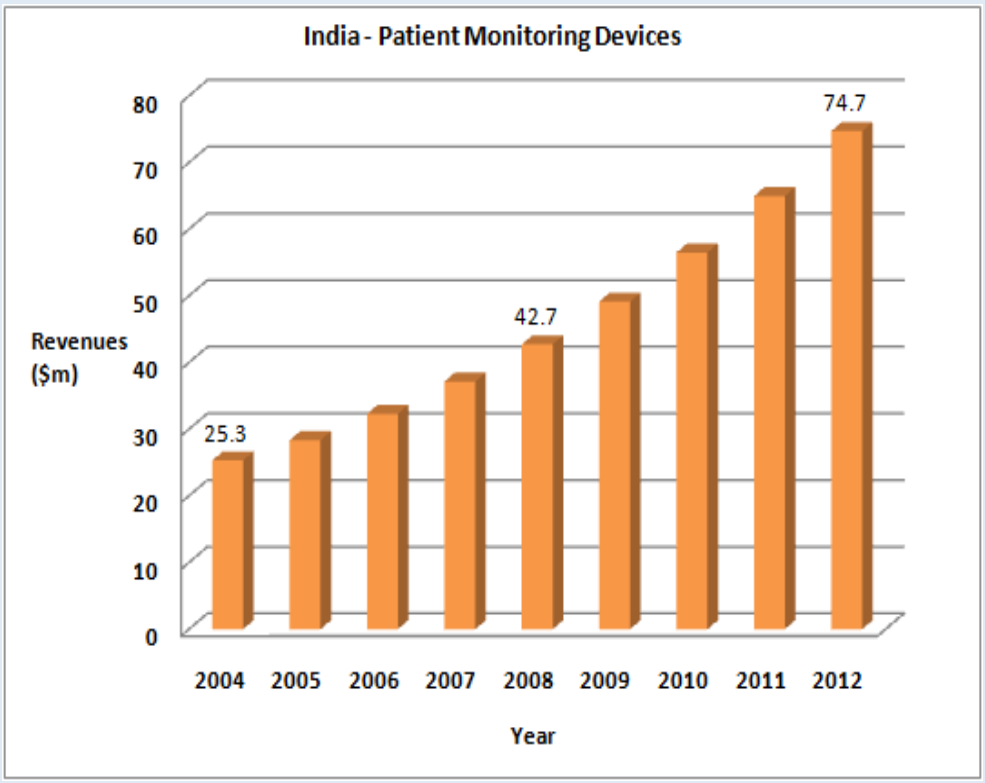
Patient Monitoring Devices - Competitive Landscape

Large number of domestic manufacturers operating in the patient monitoring device market

The major players in this segment are Philips Electronics India Limited, GE Healthcare, L&T-Medical Equipment and Systems, BPL India Limited, Schiller Healthcare (India) Pvt. Ltd., Mindray Co. Ltd., Concept Integrations (I) Pvt. Ltd, Erkadi Systems, Huntleigh, and Meditronics Healthcare Systems.

Other players include Advanced Micronic Devices Ltd. (AMDL), AKAS Medical Equipment, Allied Medical Limited, Bafna Healthcare, Bangalore Medical Systems (BMS), Chayagraphics India Pvt. Ltd., Clarity Medical, Criticare Systems, Draeger Medical India Pvt Limited (represented by HL Medical), Edan Instruments (China), EMCO Meditek, Helix Corporation, KM Biomed, Kody Medical, Krishna Medi (Bionet), Instromedix (India) Pvt Ltd (Mindray), Life Plus Medical Inc., Medical Engineers, Maestros Mediline, Nasan Medical Electronics Pvt Ltd, Nidek Medical India Pvt. Ltd., Recorders and Medicare, Rohanika Electronics,

Chart 3 - Indian Patient Monitoring Device Market, 2004-2012



Source: Veracity Health analysis

In Vitro Diagnostics - India

Indian IVD market growing at a healthy 12-15% per year

While some of the segments are witnessing faster growth rate, the overall IVD market in India has been growing at a CAGR ranging between 12 percent and 15 percent, and this trend is expected to increase moderately in the near future. With increasing emphasis being put on a preventive healthcare model, molecular diagnostics has witnessed significant growth over the last 2 years.

Accreditation of rural laboratories set to rise, increasing access to higher quality diagnostic testing outside the main urban conurbations

In rural areas, many laboratories or hospitals are still performing the diagnostic tests by semi automated analyzers or even manually. Presently, with the establishment of accreditation, a growing number of laboratories means that there will be an increase in demand for automated, smaller, faster, and easily accessible instruments. This shift to laboratory automation will become a trend from city to rural area.

In Vitro Diagnostics - Competitive Landscape

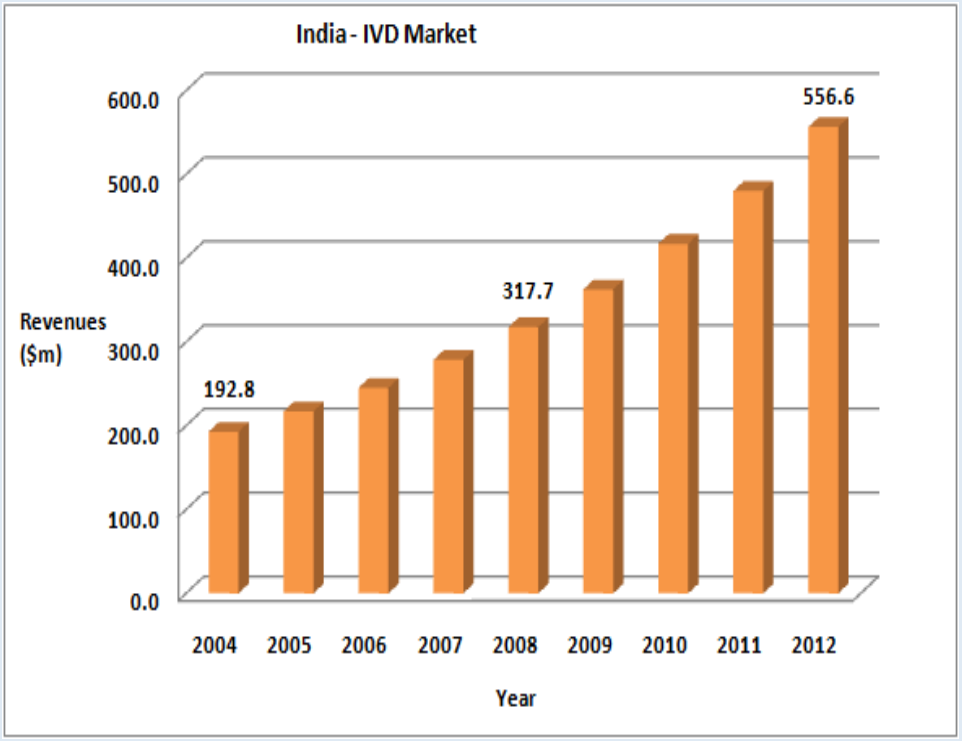
The IVD market in India was initially dominated by foreign companies; however, a large number of Indian vendors have now entered into this market. The presence of indigenous manufacturers may ultimately lead to the development of lower priced products but without compromise on quality.

Low-cost reagent kits manufactured in India and those imported from countries like China, Taiwan, and Korea are finding an increasingly receptive market. Currently, 65-70% of market revenues are accounted for by the major multinational IVD companies, namely Roche Diagnostics, Abbott, J&J, Siemens Healthcare Diagnostics, Beckman Coulter, bioMerieux, BD Diagnostics, Sysmex, and Bio-Rad.

IVD market in India dominated by the major MNCs.

Most of the remaining market share is distributed amongst the domestic manufacturers, notably - J. Mitra, Trivitron, Accurex, Tulip/Crest, Agappe, Span, Diagnova - RFCL, Transasia, and Ranbaxy.

Chart 4 - Indian IVD Market, 2004-2012



Source: Veracity Health analysis

Veracity Health analysis suggests IVD market to rise to $556m by 2012

Planned spending of $123bn on healthcare insurance coverage and infrastructure felt by some to be insufficient to reform and modernise Chinese healthcare system

SMRA International, Spacelabs Healthcare, Trivitron Healthcare Pvt. Ltd. (Nihon Kohden), and Zeal Medical.

CHINA

The healthcare system in China is primarily based on public service provision, but with a large private financing component.

The State Council's health care blueprint, which proposed the injection of $123bn into the system through 2011, will see much of the money and effort focused on providing 90% of the population with basic health insurance coverage within three years. Services beyond basic health care remain out of reach for the majority in China; reflecting an understanding of this, the government recognizes that private health insurance will have to play a greater role within the supplemental insurance system. China has been expanding the number of people covered under the Rural Cooperative Medical Scheme, which in 2007 covered 82.8% of the rural population - equivalent to 720m agricultural households.

In line with efforts targeting healthcare funding, a key push by the Chinese government is toward addressing the crumbling and dated hospital infrastructure in rural and urban clinics and community health centers. Plans are for heightened activity in new hospital construction and the purchase/upgrading of cur-

Parameters	China
Health System/Infrastructure	Medical facilities in China are mostly publicly owned: approximately 89% of the hospitals are public. According to the PRC Ministry of Health, there were approximately 18,700 hospitals and 41,700 healthcare clinics in China in 2005. The hospitals, which on average had about 130 beds, can be further divided into roughly 950 large-sized (Tier III) hospitals, 5,200 medium-sized hospitals (Tier II) and 12,500 small-sized hospitals (Tier I), respectively. Average of 322 new hospitals built each year during 1990 - 2007. This number is expected to go up to 400 annually in the next 10 years. About 30% of total investment in these new hospitals is used for purchasing medical equipment.
Public vs. Private Healthcare	2.85 million patients were served by private hospitals in 2007 – almost double the 1.5 million served in 2003. The China Insurance Regulatory Commission valued private health insurance at $8.6bn in 2008, up from $3.8bn in 2004.
Healthcare Reforms/Initiatives	
2006	The National Development and Reform Commission (NDRC) announced plans to cover all Chinese citizens under a health insurance plan by 2010.
2007	Implementation of a new five-step procedure for drug pricing aimed at increasing transparency and elimination of corruption within its system. Cost control of the State's drug bill is being tackled by the announced generation of a list of 300 – 400 basic drugs to be distributed under government control, thereby reducing the cost for customers.
2008	Introduction of a new policy to prevent doctors from over-prescribing medicines. Under the planned reform, patients will not have to pay the extra fees (ranging between 7 – 15%) that state-owned hospitals charge on medicines.
2009	China's State Council unveiled a plan to provide RMB850 billion ($123bn) to its healthcare system by 2011. The plan envisages the following steps: • Covering the entire rural and urban population under the basic medical insurance system. • Improving services of healthcare facilities in rural areas, townships, and less developed cities and reforming public hospitals in terms of their services and administration.

Government reforms targeting the build of 2,000 county-level hospitals and 2,400 health service centers in urban areas

rent medical equipment. Specifically, the Chinese government has revealed objectives to develop a national network of health care providers, building a hospital for every county. There are provisions to build at least 2,000 county-level hospitals and 2,400 health service centers in urban areas, as well as to renovate 3,700 community clinics and 11,000 urban health service centers.

Of the current planned government (2006-2010) expenditures, the early spend has focused on renovation of buildings, so spending on medical devices has thus far been relatively modest and thus still nascent.

While short-term spending on health care reform will focus on insurance and infrastructure, we believe that the medical devices industry is a natural long-term beneficiary of the reforms, given the sheer volume of medical devices that will be required to equip this new infrastructure. In addition, with the rise in chronic diseases it is safe to assume that the government will encourage more prevention and early diagnosis, meaning that imaging equipment, diagnostic reagents and vaccines manufacturers will undoubtedly benefit.

Credit Suisse estimates the market for medical devices in China will grow at 20-25% per annum over the next three years. The US Department of Commerce has a more modest 10-15% estimate, which still represents attractive growth prospects.

Medical Device Marketing and Distribution in China

Hospitals in China purchase a majority of their medical devices and supplies through distributors. Medical device distribution is highly specialized and localized in China. Most medical device distributors operate within relatively small territories; few distributors are willing or able to cover the entire country. Instead, most distributors focus on China's eastern coastal cities, where purchasing power is concentrated, while western China tends to have very limited coverage.

Hospital builds and renovations in Tier II cities is expected to drive the growth of the medical device markets in these cities

Although Shanghai and Beijing are established markets, significant opportunities exist in rapidly growing second-tier cities. Fourteen of China's rapidly growing second-tier cities together account for just 8% of China's population, but 53% of China's total volume of imports.

Top regional markets for medical devices are Tianjin, Nanjing, Shenzhen, and Chongqing - the first three ranking among the wealthiest second-tier cities in China. Hospitals in these cities have better financial resources, increased purchasing power and are more receptive to foreign products. Shenzhen is a key market with its high GDP/capita and receptiveness to new technologies and foreign brands. Chongqing offers good mid-term potential because of its large population and relatively low penetration of high-tech products at present.
The government is encouraging local medical device makers to gain market share. Initially when restrictions were eased on the imports of medical devices in the 1980s, the market was dominated by foreign products. It is estimated that over 50% of medical equipment in China is currently foreign made. Meanwhile, China has built up a domestic industry which comprises as many as 14,000 companies in this sector; it is no surprise therefore that the Chinese government is seeking ways to support home grown players as their capabilities improve.

Domestic manufacturers are also able to develop high-quality devices at a cost basis 30% lower than that of foreign competitors.

Those China-based companies that are able to develop and manufacture more advanced products at lower costs than their international competitors should be able to capitalize on the growing desire for better quality of care in China, and emerge as leaders in domestic medical device manufacturing.

Cost structures for China medical devices manufacturers are competitive compared with western counterparts, thus Chinese manufacturers are better placed to weather pricing pressures and potentially benefit from substitution to cheaper alternatives.

Pharma also to benefit from reforms aimed at wider health insurance coverage

As health insurance coverage is expected to rise so will the fortunes of the pharma companies operating in the market

The pharmaceutical industry is likely to be one of the big winners from increased health insurance coverage in China. This particularly applies to local drug manufacturers, as 102 of the 307 drugs on the new essential drugs list are traditional Chinese medicines. Inclusion on the government's list is good news and a potential sales windfall for many companies.

The Ministry of Health (MOH) has drafted the `Administrative Method of the Usage of Essential Drugs in Medical Institutions.' According to the document, retail pharmacies and all public medical institutions should stock essential drugs and are encouraged to use them. At grassroots institutions, sales of essential drugs should comprise at least 70% of total pharmaceutical sales.

Novartis plans to double its sales force in China in readiness for expansion of the market

The government will place drug stock and sales restrictions on essential drugs in Tier-two and Tier-three hospitals. Tier-two hospitals should stock 90% of drugs on the national essential drug list, and tier three hospitals should stock more than 80% of drugs on the national list. If provincial governments wish to add non-listed drugs onto their own essential drugs lists, the sales of these locally-added (non-nationally listed) drugs should not be more than 30% of total essential drug sales.

<u>Analysis of select medical device markets - China</u>

Ultrasound Market - China

Similar to global trends the color imaging market accounted for the bulk of sales in China. This segment represented about 70% of total sales in 2008. We expect the black and white machines to continue be replaced by the color machines.

Ultrasound (Colour) Market CAGR (2004-2012) 7.7%

Ultrasound (Grayscale) Market CAGR (2004-2012) 1.6%

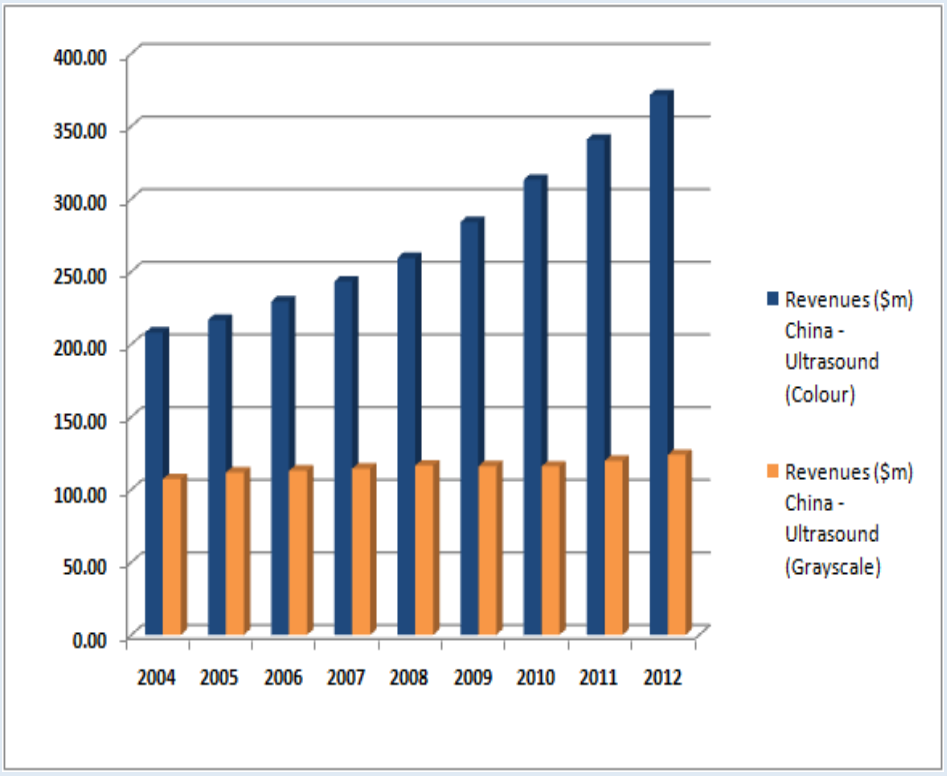
Ultrasound Market - Competitive Landscape China

Mindray has the dominant market share in the ultrasound market in China. GE and Siemens are the major challengers. Other competitors include Aloka, Teknova, SIUI and Chison.

Color doppler ultrasound will gradually replace grayscale ultrasound sales in the Chinese Market

Color ultrasound systems forecast to have a market value exceeding $350m in 2012

Chart 5 - China Ultrasound Market, 2004-2012



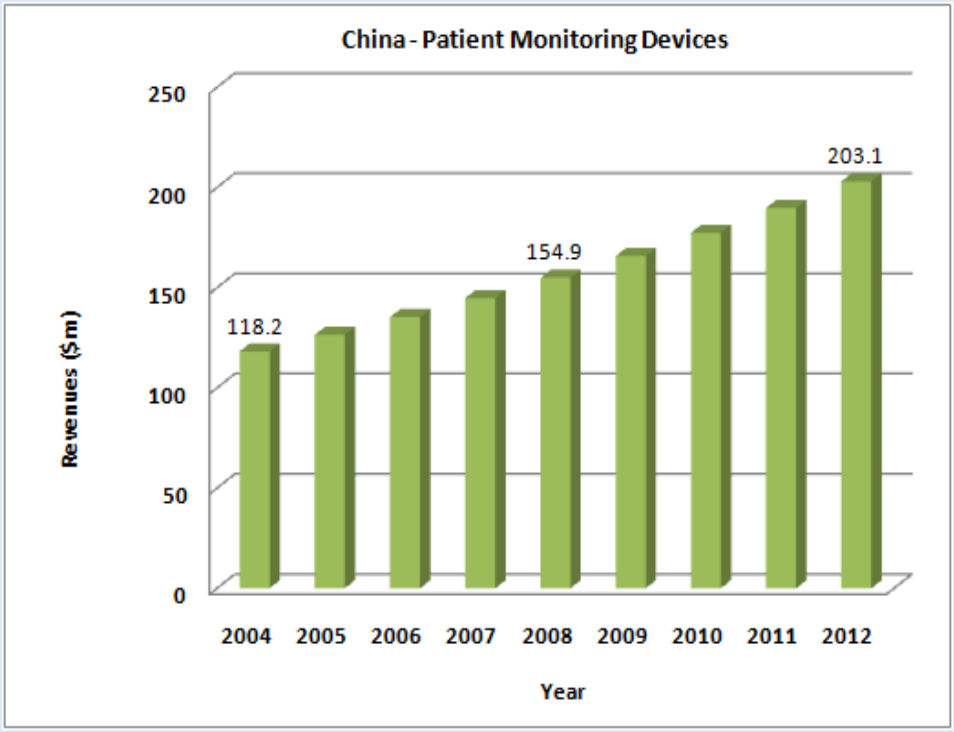
Source: Veracity Health analysis

Patient Monitoring Devices - China

The PMD market in China is expected to grow at an annual rate of 7%, according to the market leader in this space, Mindray.

Patient monitoring devices growth at 7% per annum forecast to lead to a market value of $203m by 2012

Chart 6 - China Patient Monitoring Devices Market, 2004-2012



Source: Veracity Health analysis

Patient Monitoring Devices - Competitive Landscape China

Mindray has the largest market share (by units and revenues) in China, ahead of Phillips and GE. Mindray is quite well entrenched in this market and is unlikely to see significant challenge to its position but rather we expect it to increase its market share.

In Vitro Diagnostic Market - China

The domestic manufacturer Mindray is the leading player in the Chinese patient monitoring and IVD markets

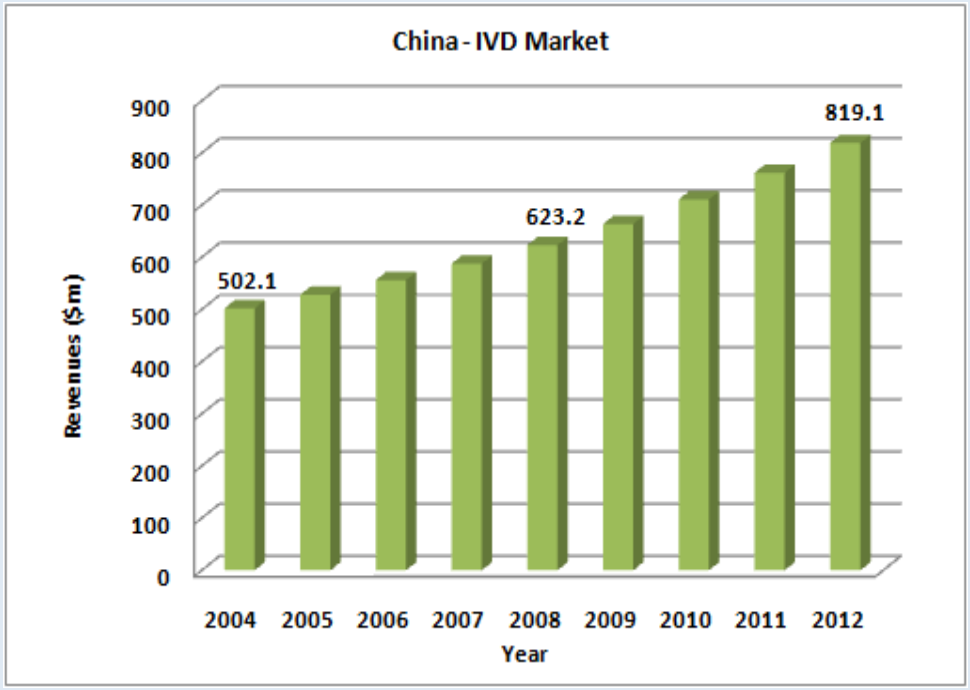
Looking only at the clinical biochemistry and hematology automated systems, the biochemistry analyser market is growing at 10% per year over the forecast period. The 5 -part hematology analyser market is growing by 7% per year and the 3-part analyser market by 5% per year.

In Vitro Diagnostic Market - Competitive Landscape China

Mindray has dominant shares in both the biochemistry market and in the 3-part and 5-part hematology market. The main competitors are multi-national companies such as Abbott, Sysmex, Hitachi, Toshiba, and Beckman Coulter.

Chart 7 - China IVD Market, 2004-2012

The IVD market in China is forecast to reach $819m in 2012



Source: Veracity Health analysis

In following issues of *Synopsis* we will continue to assess the fascinating development of the pharma, biotech and medical device sectors within the BRIC markets.

H1N1 Flu Pandemic Underscores the Role of Adjuvants in Immunization

The pandemic novel influenza virus A(H1N1), formerly known as swine flu, is expected to produce a second wave of influenza some time in October 2009. The World Health Organization (WHO) has predicted that as many as two billion people may eventually become infected with this virus.

An adjuvant is an agent that, if taken by itself, has no effect, but which can be used to positively modify the immunogenicity of a vaccine

Although A(H1N1) vaccine manufacturers CSL, GSK, MedImmune, Novartis and Sanofi Pasteur are producing the vaccine as quickly as possible, by mid-October 2009, when the vaccine is expected to become available, stockpiles will still fall far short of the number who fall into the priority subsets. The judicious use of adjuvants may help to bridge this gap. Although adjuvanted influenza vaccines have been in use in other regions, such as the EU, for a number of years, no such vaccine has been yet approved by the FDA for use in the US.

Priority subsets: hundreds of millions of people worldwide

The initial target of vaccination efforts, according to the CDC's Advisory Committee on Immunization Practices (ACIP), should be those subsets of persons—hundreds of millions of people worldwide—felt to be at greatest risk of infection or flu-related complications. These include:

- Pregnant women
- Persons who live with or provide care for infants younger than six months
- Healthcare and emergency medical services personnel
- Children and young adults aged 6 months to 24 years
- Persons aged 24 to 64 years who have concomitant medical conditions which put them at higher risk of developing flu-related complications.

Spotlight on adjuvants

The WHO has recommended that adjuvants be used in the H1N1 vaccines in order to increase the global supply

An adjuvant is an agent that, if taken by itself, has no effect, but which can be used to modify the effects of a drug or vaccine. In immunology, adjuvants are often added to an antigen to produce a more vigorous immune response. Adding such an adjuvant allows successful immunization to be induced with a smaller amount of antigen. This type of dose-sparing would allow the vaccination of a larger number of people than if an adjuvant weren't utilized. Hence adjuvants may be employed to stretch out the volume when the manufacturing yield of a vaccine is low, or can boost the vaccine's action if the vaccine demonstrates lower immunogenicity than developers had hoped to achieve, or both. Adjuvants may also decrease the unit cost of a vaccine—an important point, especially for vaccination programs in developing countries.

The most common adjuvants for use in human vaccines are aluminum salts, primarily aluminum hydroxide and aluminum phosphate, virosomes and oils. Alum was first used very widely during the 1950s as part of the poliomyelitis vaccine. During the ensuing fifty years, adjuvants have come to be used in a number of common vaccines, including DtaP (Diphtheria/Tetanus/Pertussis), hepatitis, hemophilus influenza (Hib), typhoid and some flu vaccines approved and administered in the EU.

The WHO has recommended that adjuvants be used in the H1N1 vaccines in order to increase the global supply. If current clinical trials of A(H1N1) flu vac

Table 3 - US Orders for Bulk Supply of H1N1 Influenza Vaccine Antigen and Adjuvant: May 22, 2009

Manufacturer	Bulk Vaccine Antigen	Bulk Virus Concentrate/FFF	Oil-In-Water Bulk Adjuvant
Novartis	$346,334,450	$0	$343,810,470
GlaxoSmithKline	$0	$0	$71,400,000
Sanofi Pasteur	$61,425,000	$0	$0
CSL Biotherapies	$0	$0	$0
MedImmune	$0	$61,008,000	$0
Total	**$407,759,450**	**$61,008,000**	**$415,210,470**

Source: https://www.medicalcountermeasures.gov/BARDA/MCM/panflu/

Table 4 - US Orders for Bulk Supply of H1N1 Influenza Vaccine Antigen and Adjuvant: July 9, 2009

Manufacturer	Bulk Vaccine Antigen	Oil-In-Water Bulk Adjuvant
Novartis	$150m	$139m
GlaxoSmithKline	$38m	$144m
Sanofi Pasteur	$191m	--
CSL Biotherapies	$180m	--
MedImmune	$90m	--
Total	**$649m**	**$283m**

Source: https://www.medicalcountermeasures.gov/BARDA/MCM/panflu/

cine indicate that the vaccine is poorly immunogenic, or if indications of a substantial increase in flu severity appear, then the FDA may consider emergency use authorization (EUA), allowing the addition of adjuvants to the A(H1N1) flu vaccine. If this becomes the case, then once the emergency has passed, the temporary market authorization would vanish, and the adjuvanted vaccines would be required to comply with the usual FDA drug application processes. The US government has already ordered adjuvants, Including Novartis' MF59, to stockpile for possible use with the 2009 A(H1N1) flu vaccine.

Adjuvants: Playing a crucial role in vaccine development

In the past, many vaccines were developed using whole attenuated or inactivated pathogens. Today, most vaccines under development are based on well-defined molecular immunogens, in order to decrease problematic reactogenicity. While these vaccines are based on viral vectors known to be safe for humans, they usually are not as immunogenic as vaccines of the past. These new vaccines therefore *require* adjuvants in order to induce the desired immune response and protection. In addition, newer vaccines often need to trigger a strong cellular response, such as the induction of T helper cells and cytotoxic T lymphocytes, as well as antibodies. Traditional adjuvants based on alum salts mostly induce simply an antibody response.

Strategies: Acquisition or licensing of an adjuvant

The vaccines market over the last few years has seen a surge in activity, and as a result, interest has sharpened in the discovery and development of new adjuvants. For a medium to large-sized pharma-biotech company which develops vaccines, one useful strategy would be to acquire a small biotech which has a novel adjuvant in a later stage of development—especially if that adjuvant has demonstrated favorable results when tested with the pharma company's vaccine. For example, in 2005, GSK spent $300 million to acquire Corixa, which had created the novel vaccine adjuvant MPL.

Smaller companies are understandably looking for partnerships with global vaccine manufacturers

Another option, particularly well-suited to small companies with adjuvants in development, would be to out-license an adjuvant to a larger company. A number of large biotechs have licensed promising adjuvants developed by others, including: Sanofi Pasteur with Eisai's E6020, a TLR-4 (Toll-like receptor-4) agonist; Wyeth (now owned by Pfizer) in 2006 with Intracell's synthetic adjuvant IC31; and in 2007, Novartis, when it gained exclusive access to IntraCell's IC31 adjuvant.

A review of current news events regarding adjuvants for influenza vaccines, by company:

Global players busy with in-house adjuvant developments

CSL Ltd.
In July 2009, Australian company CSL began testing its H1N1 vaccine in Australia. CSL's proprietary adjuvant, Iscomatrix, is a phospholipid-cholesterol formulation containing a purified saponin extract from the bark of the South American tree *Quillaja saponaria*, with both antigen delivery and immunomodulatory capabilities. The company has evaluated a range of **Iscomatrix** adjuvanted vaccines in clinical trials which indicate that the Iscomatrix adjuvant is safe and generally well tolerated and increases the vaccine immune responses. CSL has several license and option agreements involving Iscomatrix with major vaccine manufacturers including Merck & Co., Wyeth and Novartis. These licensing agreements also stipulate that CSL will be the worldwide supplier of this adjuvant. It was in order to meet manufacturing demand for Iscomatrix that CSL built a plant at Kankakee, IL in the US.

GlaxoSmithKline Biologicals
GSK's (H1N1) 2009 adjuvanted vaccine will consist of two vials: the H1N1 2009 pandemic flu antigen, and GSK's proprietary **AS03 adjuvant system.** The contents of the two vials will be combined before administration. GSK has other proprietary adjuvant systems, including AS02 and AS03.
These adjuvant systems consist of traditional adjuvants mixed with immunomodulators which have been specifically tweaked to the antigen and the target population. According to GSK, in clinical evaluations AS04 has shown success in a number of vaccines against viral diseases. AS02 and AS01 have been developed for use where a stronger T-cell response is required.

Novartis AG
Probably Novartis' best-known adjuvant is MF59, which it obtained when it acquired Chiron. Novartis has been testing MF59 and administering vaccines manufactured using this adjuvant for over ten years. According to the company, over 40 million doses of the adjuvanted seasonal flu vaccine, Fluad®, have been distributed in the EU since 1997. Fluad is not licensed for the US market. In early September 2009, the company reported that it had begun testing its swine flu vaccine in about 6,000 people in Britain, Germany and the U.S. In the US, Novartis is testing both adjuvanted and unadjuvanted vaccines.
According to a study published in May 2009 in the *Proceedings of the National Academy of Sciences* (USA), Novartis' investigational pre-pandemic avian influenza vaccine, Aflunov®, created using MF59, is able to produce a broadly cross-reactive immune

response which covers all known H5N1 antigenic variants, even if the booster dose is given six years after the initial dose. Researchers believe that one important characteristic of any pre-pandemic vaccine is that it be able to demonstrate cross-reactivity because of the strain variations that can occur in any emerging influenza virus.

Sanofi Pasteur

In July 2008, Sanofi Pasteur and 3M Drug Delivery Systems announced an agreement in which 3M would provide its patented toll-like receptor (TLR) agonist compounds to Sanofi Pasteur for use as vaccine adjuvants. In developing a vaccine against H5N1, Sanofi Pasteur selected an alum adjuvant to boost immunogenicity. The company is evaluating other adjuvants for use in H5N1 and H1N1 vaccines.

In August 2009, Sanofi Pasteur submitted a supplemental application to the FDA for licensure of the influenza A(H1N1) 2009 monovalent vaccine. The application specifies the evaluation of a non-adjuvanted vaccine. The company will be gathering data on Immunogenicity and safety, as well as evaluating the safety and potential benefits of adding an adjuvant to its vaccine.

Table 5 - Vaccines being developed with adjuvant technology

Company	Developments
3M Public; www.3m.com	TLR agonists licensed to Celldex Therapeutics for use as adjuvants
Alba Therapeutics Private; Baltimore MD, USA; www.albatherapeutics.com	Dedicated to the development and commercialization of disease-modifying therapeutics to treat autoimmune and inflammatory diseases, drug delivery agents and mucosal vaccine adjuvants.
Antigenics Public; Lexington MA, USA; www.antigenics.com	Developed QS-21, the leading member of the Stimulon family of adjuvants; has been shown to stimulate both antibody (humoral) as well as cellular immune responses.
Coley Pharmaceuticals Acquired by Pfizer in 2008	Publicly-held biopharmaceutical company specializing in vaccine adjuvant technology and a new class of immunomodulatory drug candidates designed to fight cancers, allergy and asthma disorders, and autoimmune diseases.
Corixa Corporation Acquired by GSK in 2005.	Corixa was acquired for its work in developing innovative adjuvants designed to stimulate immunity.
Crucell Public; Leiden, The Netherlands; www.crucell.com	Has developed virosomes, a proprietary delivery system with adjuvant properties; shows excellent tolerability while stimulating both arms of the immune response, and used in two marketed vaccines. Also has developed mucosal adjuvants for intranasal and transcutaneous vaccination.
CSL Behring Public; King of Prussia, PA, USA; www.cslbehring.com	Iscomatrix adjuvant—use in vaccines, outlicensing; development of additional adjuvants.
Cytheris SA Private; Paris, France; Rockville, MD, USA; www.cytheris.com	The company's product family strengthens innate and adaptive immunity connections and will provide new immuno-therapeutic adjuvants for cancer and chronic infectious diseases.
GSK Biologicals Public; www.gsk.com	One of leaders in adjuvant technology. Proprietary adjuvant system AS03 used in formulating H1N1 vaccine. Others include AS02A, AS01, AS04.
Idera PharmaceuticalsPublic; Cambridge MA, USA; www.iderapharma.com	Developing drug candidates to treat cancer and infectious, respiratory, and autoimmune diseases, and for use as vaccine adjuvants.
Immune Design Public; Seattle WA, USA; www.immunedesign.com	Identified improved adjuvants and novel technologies targeting and controlling dendritic cells.
Intercell AG Public—one of last large independent vaccine companies; Vienna, Austria; www.intercell.com	Novel adjuvant vaccine enhancement patch uses a protein from the toxin produced by E. coli bacteria; expected to show mid-stage data in late 2009; looking for potential marketing partner in coming months for the company's adjuvant patch meant to bolster vaccines against the H5N1 bird flu virus. Others in development include vaccine patches for H1N1 and traveller's diarrhea, using different formulations of same adjuvant. Another Intercell adjuvant is IC31, which induces T-cell and B-cell responses by using a unique synthetic formulation which combines the immunostimulating properties of an anti-microbial peptide, KLK, and an immunostimulatory oligodeoxynucleotide, ODN1a.
Juvaris BioTherapeutics Private; Burlingame CA, USA; www.juvaris.com	Has been awarded multiple NIH grants including 2007 award for approximately $9M to develop adjuvants for influenza vaccines.
Novavax Public; Rockville MD, USA; www.novavax.com	The company's technology platforms include the virus-like particle (VLP) manufacturing technology utilizing the baculovirus expression system in insect cells, as well as novel vaccine adjuvants based on Novasomes®, non-phospholipid vesicles and dendrimer technologies.
Oncothyreon (formerly Biomira) Public; Seattle WA, USA; www.oncothyreon.com	Business development efforts include discussion of Pet lipid-A, a toll-like receptor 4 (TLR4) agonist, manufactured as an adjuvant for vaccine formulations for clinical trials.

Table 6 - Vaccines being developed with adjuvant technology

Company	Developments
Sanofi Pasteur Public; Lyons, France; www.sanofipasteur.com	Investigational H5N1 pandemic influenza vaccine contains a proprietary adjuvant; achieved a high immune response at low dose of H5N1 antigen. Exploring other, alternative adjuvants.
SciClone Pharmaceuticals Public; Foster City, CA, USA; www.sciclone.com	Zadaxin, the Company's brand of thymalfasin and its primary product, is sold in over 30 countries for the treatment of the hepatitis B virus (HBV) and the hepatitis C virus (HCV), certain cancers and as a vaccine adjuvant.
Tolerx Private; Cambridge MA, USA; www.tolerx.com	Two pre-clinical candidates, TRX518 and TRX385, that enhance immune responses and are being evaluated for potential benefit in the treatment of cancer, chronic viral diseases, and as vaccine adjuvants.

KEY OPINION LEADER INTERVIEW

Prof Timo Vesikari, Director, Vaccine Research Centre, Medical School, University of Tampere, Finland. 1991-present Professor of Virology, University of Tampere, and Consultant Paediatrician (Paediatric Infectious Disease), Tampere University Hospital. Professor Vesikari was responsible for leading a team which carried out the first clinical trial of rotavirus vaccine in humans in 1982-1983. In 1987-1990 he did research on diarrhoeal disease vaccines and clinical trials in developing countries as part of the Diarrhoeal Control Programme of WHO and has served on many WHO Steering Committees and Scientific
Working Groups. Professor Vesikari is former Chairman of The Finnish Society for the Study of Infection, and Bill Marshall lecturer of European Society for Paediatric infectious Diseases (ESPID). Professor Vesikari's paper on the rotavirus vaccine trial (REST), published in the New England Journal of Medicine (NEJM), was declared the 2007 Paper of the Year by The Lancet.

Veracity Health had the distinct pleasure of being able to briefly interview Dr. Timo Vesikari regarding some of the most important issues in vaccines today. What follows is a transcript of that interview.

VH: Thank you for agreeing to speak with us, Dr. Vesikari. I would first like to ask you a general question: what do you consider (apart from A/H1N1 and H5N1) to be the disease area(s) of greatest need today, and how far away is the commercialization of vaccines for these highest-priority diseases?

One high priority need for a vaccine, and something which is common in all corners of the world, is respiratory syncytial virus, RSV. That always comes to mind first when you ask this question of pediatricians, and as I'm a pediatrician, I immediately raise this as an issue of concern. There are so many problems with developing a vaccine for RSV, and it's difficult to think of a suitable vaccine candidate in terms of how it should be constructed. Additionally, it's very difficult to think of an immunization program that would effectively target the risk pool which specifically comprises prematurely-born children. But still, a development of vaccines against RSV is a priority. We have some candidates, in Phase I, very early stages.

VH: As far as you understand, then, it's much too early to say whether any of these candidates will be coming on the market in 10-12 years.

Yes, this is my view. There is one vaccine at early stage of testing in humans, but there's no evidence whatsoever that it would actually work. Furthermore you have to consider the other issues I mentioned, can you test and target the vaccine at the correct cohort of patients, notably prematurely born infants. Certainly in terms of need, RSV is undoubtedly on the top of the priority list.

VH: What other areas of need are there, perhaps your top three areas of need?

Meningococcus B is something that companies are working towards and which clinicians desire. There are candidate vaccines from Novartis and Wyeth. From a pediatric perspective, this is clearly a need, one on a global scale. There is a need for MenB vaccine also later in adulthood. The vaccine candidates are advanced in terms of their clinical development, but not necessarily ideal. Both vaccines appear somewhat reactogenic. We are not entirely clear on their potential efficacy, but they are the candidates that we have at the moment. Due to the serious nature of meningococcal disease and the mortality

associated with it, this is an area which would benefit greatly from the commercial introduction of an effective vaccine.

To phrase it in a generic way, we would need a vaccine that prevents or significantly reduces otitis media. Extended spectrum conjugate pneumococcal vaccine and vaccine against non-capsulated *Haemophilus influenzae* would be one part of this, and a vaccine against major respiratory viruses the other part.

VH: So otitis media is cause by multiple pathogens, and there are vaccines, but they are not particularly effective?

Right. RSV could be part of it, influenza might be part of it, but then there are other respiratory viruses that might be important to include in such a vaccine, like a multiple respiratory tract pathogen vaccine. In terms of disease burden in developed countries also—such as the United States and Europe—this is where there is a lot of need and it could be done better. We need to target otitis media with a more efficient polyvalent vaccine.

VH: What about the developing countries? What about malaria and cholera? Are there effective vaccines against these diseases?

These are totally different. Cholera is not a disease of young children. Cholera vaccines, though not highly effective, have been around for 20 years. The track record is that they are not being used very much. So there might be a need, but it's very difficult to predict when and where the vaccine should be used, and there are other ways of controlling cholera. I'm not really sure that this is an area in which there is so much that can be done to improve the current vaccines, or to increase vaccination.

On the other hand, when you consider malaria, especially in Africa, there is clearly a need for a malaria vaccine, especially for children. The mortality is so high (a million deaths a year) that an effective vaccine would do a lot to prevent deaths in children in Africa. The GSK vaccine has efficacy between 30- 50%. Even such a modest reduction is great in terms of prevention of deaths. With malaria, there is no question of the need, and if an effective vaccine were around, it would not only be used, but it would be recommended by the international health organizations.

VH: On a somewhat different subject, I have read that there are companies working on vaccines against *C. difficile*.

It's a disease of, say, developed countries. It's a hospital issue, and whether it's preventable by vaccine, I'm not really sure. However, there are many other areas for vaccines that are targeting hospital infections, like pseudomonas and maybe ***Staphylococcus*** *aureus*, and none of them have reached an advanced stage. Because these are issues associated and reported widely in developed countries and modern hospitals, and there may be a market and an audience that can pay for effective vaccines.

VH: Could you tell us a bit about where you think the production technology will be in 5-10 years?

You mean the viral vaccines? The egg-based technologies are only used for influenza vaccines.

Egg-based production is still fairly convenient and maybe even sufficient in the case of the annual seasonal flu vaccine, but if there's greater need than that, like in the present H1N1 situation, this technology will not be sufficient to produce enough vaccine. So the companies that can produce the same vaccine in cell culture have a certain advantage. I believe they can handle much greater production volumes. Because cell-based technology doesn't offer any other advantage, the efficacy of the vaccine or the safety of the vaccine aren't any better, the egg-based vaccines will continue to be produced.

VH: I understand that the big advantage of the cell-based technology is that it's so much faster.

It *is* faster, and it may be cheaper on a large scale, but I don't think the companies are going to charge less for the vaccine. So it won't turn out to be cheaper for the consumer. Plus the flu vaccine is cheap anyway.

VH: What about H5N1?

Right now it is neglected because of H1N1, but it is still there, it is still causing this disease in birds, it is occasionally being transmitted to humans, it is still causing occasional deaths among humans. It's not extinct, it's there, it's around. I still think it's the responsibility of the governments or the authorities to be prepared for this, which means probably at some point purchasing the vaccine and keeping it in stock. From the manufacturer's viewpoint, there is a market. It doesn't go away with the appearance of H1N1.

VH: Speaking of stockpiling and preparation, I've gained the impression that governments finally, after being warned for many years, *may* be better prepared in case of a serious pandemic, meaning one with a higher mortality rate. Do you agree with this, or is this more like political show?

I'm not sure that the governments are really much better off or much better prepared, *except* for stockpiling. And whether the vaccines in stock, or the anti-viral drugs in stock for that matter, turn out to be of much use, I can't say. However, the governments are not better off in terms of having, say, more hospital beds or intensive care unit beds, for example. So should a pandemic happen and a lot of people fall seriously ill, the capacity of all countries would be exceeded very quickly. The healthcare infrastructures around the world are not adequately equipped to handle a pandemic even with the stockpiling of sufficient quantities of vaccine.

VH: Thank you for your time, Dr. Vesikari. It has been a pleasure talking with you!

Companies developing vaccines for the diseases mentioned: Cholera, *C. difficile*, Influenza (seasonal, H1N1, H5N1), Malaria, Meningococcus, Otitis media, Pneumococcus, RSV, *S. aureus*, and streptococcus.

The following tables highlight the vaccines in development for these diseases

Table 7 - Companies developing Influenza Vaccines

Manufacturer	Indication	Product Name	Development Status
Influenza Vaccines			
Celldex Therapeutics	Cholera	CholeraGarde® cholera vaccine live attenuated	Phase II
Celldex Therapeutics	Cholera	CholeraGarde® cholera vaccine	Phase II
Acambis (acquired by sanofi pasteur; partnering with Antigenics)	Flu virus prevention	ACAM FLU A	Phase I
sanofi pasteur	H1N1 pandemic vaccine	Influenza A(H1N1) 2009 monovalent vaccine	Aug. 2009--submitted supplemental application to FDA for licensure of its influenza A -H1N1, 2009 monovalent vaccine.
sanofi pasteur	H5 and other types of influenza	Flu pandemic vaccine	Phase II
sanofi pasteur	Influenza	Flu micro-injection vaccine (new delivery)	Phase III
AlphaVax	Influenza virus infections	Influenza virus vaccine	Phase I
Baxter Healthcare (partnering with DynPort Vaccine)	Influenza virus infections	H5N1 influenza vaccine	Phase I
Baxter Healthcare (partnering with DynPort Vaccine)	Influenza virus infections	Seasonal influenza virus vaccine	Phase I
GlaxoSmithKline	Influenza virus infections	H5N1 pre-pandemic influenza virus vaccine	Phase I
LigoCyte Pharmaceuticals	Influenza virus infections	Influenza VLP vaccine (seasonal)	Phase I
MedImmune (AstraZeneca)	Influenza virus infections	H5N1 avian influenza intranasal vaccine	Phase I
Merck	Influenza virus infections	V512	Phase I
PowderMed	Influenza virus infections	Influenza virus DNA vaccine (PF-4522625)	Phase I
sanofi pasteur	Influenza virus infections	Flu cell vaccine (new production method)	Phase I
Vaxin	Influenza virus infections	Influenza virus vaccine intranasal	Phase I
Vical	Influenza virus infections	Influenza virus DNA vaccine	Phase I
Merck	Influenza virus infections	Influenza vaccine	Phase I
Novavax	Influenza virus infections	H5N1 influenza virus vaccine	Phase I
GlaxoSmithKline	Influenza virus infections	Influenza virus vaccine	Phase II
Novartis Pharmaceuticals	Influenza virus infections	Pandemic influenza vaccine	Phase II

Table 8 - Companies developing Influenza Vaccines

Manufacturer	Indication	Product Name	Development Status
Influenza Vaccines (cont'd)			
Intercell	Pandemic influenza prevention	Prophylactic/vaccine Pandemic influenza vaccine patch	Phase I/II
GlaxoSmithKline	Pandemic influenza prevention	H5N1 pandemic influenza virus vaccine	Phase III
Protein Sciences	Influenza virus infections	FluBIOk™ influenza virus vaccine (rHA)	Phase II
Protein Sciences	Influenza virus infections	Influenza virus vaccine (rNA)	Phase II
Novartis Pharmaceuticals	Influenza virus infections	Optaflu® US influenza virus vaccine (flu cell culture)	Phase III
Novartis Pharmaceuticals	Influenza virus infections	Aflunov pre-pandemic H5N1 influenza vaccine	Phase III
sanofi pasteur	Influenza virus infections	Flu vaccine (new formulation)	Phase III
LigoCyte Pharmaceuticals	Influenza virus infections	Influenza VLP vaccine (pandemic)	preclinical
Novartis Pharmaceuticals	Influenza virus infections	Aflunov EU pre-pandemic H5N1 influenza vaccine	Registered.
VaxInnate	Influenza virus infections prevention	Influenza virus M2e vaccine	Phase I
Bionor Immuno	Universal influenza vaccine	Influenza	Pre-clinical

Table 9 - Companies developing Malaria Vaccines

Manufacturer	Indication	Product Name	Development Status
Malaria Vaccines			
Crucell	Malaria	Malaria vaccine	Phase I
GenVec	Malaria	Malaria vaccine	Phase I
BioSante Pharmaceuticals	Malaria prevention	Malaria vaccine	Phase I
GlaxoSmithKline	Malaria prevention	Mosquirix™ malaria recombinant vaccine	Phase III

Table 10 - Companies developing Meningococcal Vaccines

Manufacturer	Indication	Product Name	Development Status
Meningococcal Vaccines			
sanofi pasteur	Meningitis and pneumonia in infants	Pneumonia vaccine	Phase I
GlaxoSmithKline	Meningococcal group A, C, W-135, Y infections	Meningococcal vaccine groups ACWY	Phase II
Novartis Pharmaceuticals	Meningococcal group A, C, W-135, Y infections	Menveo infants meningococcal vaccine groups ACWY	Phase III
Novartis Pharmaceuticals	Meningococcal group A, C, W-135, Y infections	Menveo adolescents meningococcal vaccine groups ACWY	Phase III
Roche	Meningococcal group B infections	Meningococcal vaccine group B	in clinical trials
Emergent BioSolutions	Meningococcal group B infections	Meningococcal group B vaccine recombinant	Phase I
sanofi pasteur	Meningococcal group B infections	Meninge B vaccine	Phase I
Wyeth Pharmaceuticals (Pfizer)	Meningococcal group B infections	Meningococcal group B vaccine (rLP2086)	Phase I
GlaxoSmithKline	Meningococcal group B infections	Meningococcal vaccine groups B/C	Phase II
Wyeth Pharmaceuticals (Pfizer)	Meningococcal group B infections	Meningococcal group B vaccine OMV	Phase II
Baxter Healthcare	Meningococcal group B infections	NeisVac-B™ meningococcal vaccine group B conjugate	Phase II
Novartis Pharmaceuticals	Meningococcal group B infections	MenB meningococcal vaccine group B	Phase III
Roche	Meningococcal group B infections, Streptococcal infections	Group B meningococcal and group B streptococcal vaccine	in clinical trials
Baxter Healthcare	Meningococcal group C infections	NeisVac-C™ meningococcal vaccine group B conjugate	Phase III
Wyeth Pharmaceuticals (Pfizer)	Meningococcal group C infections, Pneumococcal infections	Pneumococcal and meningococcal group C vaccine conjugate	Phase III
GlaxoSmithKline	Otitis media, pneumococcal infections	Pneumococcal vaccine conjugate	Phase III

Table 11 - Companies developing Parainfluenza/RSV Vaccines

	Indication	Product Name	Development Status
Parainfluenza/RSV Vaccines			
MedImmune (AstraZeneca)	Parainfluenza virus infections	MEDI-560	Phase I
Wyeth Pharmaceuticals (Pfizer)	Parainfluenza virus infections	Parainfluenza virus vaccine live, intranasal	Phase I
MedImmune (AstraZeneca)	Parainfluenza virus infections, respiratory syncytial virus infections	MEDI-534 parainfluenza/ respiratory syncytial virus vaccine	Phase I
Wyeth Pharmaceuticals (Pfizer)	Parainfluenza virus infections, RSV infections	Respiratory syncytial virus (RSV) parainfluenza virus vaccine	Phase I
Wyeth Pharmaceuticals (Pfizer)	RSV infections	Respiratory syncytial virus (RSV) PFP-1 vaccine	Phase II
Wyeth Pharmaceuticals (Pfizer)	RSV infections	Respiratory syncytial virus (RSV) PFP-2 vaccine	Phase II
Wyeth Pharmaceuticals (Pfizer)	RSV infections	Respiratory syncytial virus (RSV) vaccine, live	Phase II

Table 12 - Companies developing Staphylococcus/Streptococcus Vaccines

Manufacturer	Indication	Product Name	Development Status
Staphylococcus/Streptococcus Vaccines			
Nabi Biopharmaceutical	S. aureus infections	PentaStaph (Pentavalent S. aureus vaccine)	Aug 2009--sold to GSK for further development.
Intercell (partnering with Merck)	S. aureus infections	S. aureus prophylactic vaccine	Phase II/III
GlaxoSmithKline	Seasonal influenza prevention for the elderly	New generation flu inactivated split-trivalent vaccine	Phase III
BioSante Pharmaceuticals	Staphylococcal infections	Staph vaccine	Phase I
ID Biomedical	Staphylococcal infections	Streptococcal A vaccine	Phase I
Merck	Staphylococcal infections	Staphylococcus aureus vaccine	Phase I
Merck	Staphylococcal infections	V710	Phase I
Nabi Biopharmaceutical	Staphylococcal infections	Staph. Epidermidis vaccine conjugate	Phase I
SIGA Technologies	Staphylococcal infections	Streptococcal A vaccine	Phase I

Manufacturer	Indication	Product Name	Development Status
Staphylococcus/Streptococcus Vaccines (cont'd)			
GlaxoSmithKline	Streptococcus pneumoniae and non-typeable haemophilus influenza disease prevention for children	Synflorix™ conjugated vaccine	Submitted; approved in EU Jan. 2009; as of Q1 of 2009, "no current plan to file in US"
Wyeth Pharmaceuticals (Pfizer)	Strep. pneumoniae disease prevention	Prevnar 13	Delayed by FDA to beginning 2010.
GlaxoSmithKline	Strep. pneumoniae disease prevention	S pneumoniae recombinant-conjugated vaccine	Phase I

Novel Technologies Are Expanding Drug Delivery using Dermal Patches

The advantages of transdermal drug delivery have long been acknowledged: convenience, pain-free delivery, more consistent drug blood levels and improved patient compliance, to name a few. However, transdermal technology in general, and patch applications in particular, has been a relatively niche market, stymied by the inability to successfully deliver larger and more complex molecules across the skin barrier, due to factors such as molecule size and solubility of proteins, carbohydrates and peptides.

3rd generation transdermal drug delivery systems using novel microdermabrasion, microneedle and electroporation technologies

Recently, this scenario has begun to change. A number of companies are conducting research and development in the transdermal delivery systems (TDS) space, and significant progress has been made, especially during the last five years. First generation TDS were able to deliver small, lipophilic drugs in low doses. Second generation systems employed non-cavitational ultrasound and iontophoresis, allowing improved control of the rate of drug delivery. Third generation TDS are using technologies such as microneedles, microdermabrasion and electroporation. These developments are allowing the movement of larger, more complex molecules across the skin barrier, thus expanding the number of drugs under development for delivery via transdermal patch. In addition to the traditional patch drugs, such as scopolamine, nitroglycerin, tulobuterol, estradiol and nicotine, the list now includes fentanyl, diclofenac epolamine, clonidine, lidocaine, some antidepressants, hormonal contraceptives, vaccines, stimulants to treat ADHD, and others.

Leading technology Developers are 3M, HP and Aveva Drug Delivery Systems

When discussing transdermal patch technology, companies tend to fall into one of three areas: they are a developer of proprietary patch technology which they then license out to other companies, frequently partnering with a drug company to create the final product for the partner to market; they are a pharmaceutical company which in-licenses patch technology in order to marry it to one of their drugs; or they handle both transdermal technical development and drug development in-house. Most companies fall into the first or second categories. Among the leaders in the development of patch drug delivery technology are 3M Drug Delivery Systems, HP (leveraging its inkjet technology) and Aveva Drug Delivery Systems (a fully-owned subsidiary of Nitto Denko).

Following is a selection of recent news items from companies active in the transdermal patch drug delivery space:

September 2009

NuPathe Inc. announced the data from its Phase III trial of Zelrix™, a novel transdermal patch in clinical development for the treatment of acute migraine. Zelrix combines NuPathe's proprietary SmartRelief™ iontophoretic transdermal technology with sumatriptan. According to the company, the Phase III trial was conducted in 530 adults and was administered in a multicenter, randomized, parallel group, double-blind, placebo-controlled trial, where efficacy and tolerability of Zelrix were compared with placebo. Statistical significance on primary endpoint and all key secondary endpoints.

Pantec was granted an EU patent for P.L.E.A.S.E.® technology. In April 2009, the company announced successful results from a Phase I clinical trial of a triptorelin patch used in conjunction with P.L.E.A.S.E.® technology.

TransPharma Medical announced the successful completion of Phase 2A trial of ViaDerm-hPTH (1-34) for post-menopausal women with osteoporo sis. The drug uses TransPharma's ViaDerm transdermal delivery system.

TransPharma partnered with Eli Lilly in 2008 to commercialize the drug with the ViaDerm technology.

August 2009

Aveva Drug Delivery Systems received final approval from the US FDA for its Abbreviated New Drug Application (ANDA) for a clonidine transdermal system. The system will be manufactured by Aveva; its licensing partner, Par Pharmaceuticals, will have exclusive rights to commercialize the product in the US.

At the 238th National Meeting of the American Chemical Society, Mark Prausnitz, Ph.D, of the Georgia Institute of Technology, reported on the design of a transdermal patch lined with microneedles. This patch may someday be used to deliver flu vaccine, or for targeted delivery of drugs to the eye. Human trials of the patch are expected to begin in 2010.

May 2009

UCB announced that the European Medicines Agency's (EMEA) Committee for Medicinal Products for Human Use (CHMP) issued a positive opinion recommending that the European Commission lifts the treatment restrictions for Neupro® (rotigotine transdermal patch) in Europe.

Teikoku Pharma USA, a wholly-owned subsidiary of Teikoku Seiyaku Inc. Of Japan, announced the acquisition of Travanti Pharma Inc, a privately held corporation that has developed a proprietary Wearable Electronic Disposable Drug delivery technology (WEDD®) Platform. WEDD is an innovative electronic transdermal (iontophoretic) drug delivery system. The acquisition is part of Teikoku's core strategy to develop transdermal pharmaceutical products.

April 2009

Zosano Pharma, Inc. presented positive results from its Phase 2 study of the ZP-PTH rapid delivery patch for the treatment of osteoporosis. The study was designed to determine safety and efficacy of the ZP-PTH rapid delivery patch for the treatment of osteoporosis.

Altea Therapeutics announced that it had entered into an agreement with Eli Lilly and Amylin Pharmaceuticals, Inc. to develop and commercialize a novel daily transdermal patch delivering sustained levels of exenatide utilizing Altea's proprietary PassPort® Transdermal Delivery System.

March 2009

DURECT announced positive results from a 74 patient Phase IIb clinical trial conducted by Endo Pharmaceuticals of TRANSDUR(TM)-Sufentanil, a proprietary seven day patch under development for the treatment of chronic pain. In September 2009, Endo returned the development and commercialization rights to DURECT, which intends to follow a 505(b)2 regulatory pathway for the Phase III program and approval.

Abeille Pharmaceuticals signed an exclusive License Agreement with ProStrakan Group plc to develop and sell AB-1001, Abeille's transdermal patch for emesis, in all territories excluding Japan, China (including Hong Kong), Korea, Taiwan and Singapore. AB-1001 is a transdermal patch for chemotherapy induced nausea and vomiting (CINV).

Vyteris announced the initiation of a Phase II clinical trial sponsored by its development partner, Ferring Pharmaceuticals Inc. The trial evaluates Vyteris' smart patch technology for the safety and efficacy of a pulsatile delivery of a peptide hormone for the treatment of infertility in women.

The following table provides the names of a number of companies which are utilizing transdermal patch technology, with a brief description of their technology.

Table 13 - Companies developing transdermal patch technology

Company	Technology
Pharmaceutical/Biotech	
Abeille Pharmaceuticals www.abeillepharma.com	AB-1001 is a transdermal patch for chemotherapy induced nausea and vomiting (CINV).
DURECT www.durect.com	TRANSDUR technology, a proprietary transdermal delivery system that enables delivery of drugs continuously for up to 7 days, is the basis for TRANSDUR-Sufentanil which is currently in Phase II clinical trials.
FluGen www.flugen.com	Patented vaccine-loaded, pump-type delivery technology; exclusive rights secured by FluGen from Ratio, Inc.
Hisamitsu Pharmaceutical Co. www.hisamitsu.co.jp	Transdermal and transmucosal absorption and penetration enhancers, for use in its adhesive patch technology.
Intercell (acquired IOMAI in 2008) www.intercell.com	Vaccine skin patches to protect against traveler's diarrhea, pandemic influenza.
Noven Pharmaceuticals (acquired by Hisamitsu Pharmaceutical Co. in August 2009) www.noven.com	DOT Matrix® technology, an advanced proprietary drug-in-adhesive matrix in which the drug is mixed with the adhesive that holds the patch on the skin.
NuPathe www.nupathe.com	SmartRelief™ iontophoretic transdermal technology which uses low-level electrical energy to transport drugs through the skin.
Phosphagenics www.phosphagenics.com	Matrix Patch Technology; TPM technology, which comprises vitamin E phosphates, shown to enhance dermal, transdermal and oral absorption of compounds.
Teikoku Pharma USA www.teikokuusa.com	Through acquisition of Travanti Pharma in May 2009, acquired Wearable Electronic Disposable Drug delivery technology (WEDD®) Platform, an innovative electronic transdermal (iontophoretic) drug delivery system. Also, Hydrogel patches and Tapes (anhydrous patches).
TransPharma Medical Ltd. www.transpharma-medical.com	ViaDerm drug delivery system utilizing proprietary RF-MicroChannel Technology.
UCB www.ucb.com	Neupro® rotigotine transdermal patch
VaxInnate www.vaxinnate.com	Using patented 3M microneedle technology, called 3M Microstructured Transdermal System (MTS), to deliver its M2e universal flu vaccine using a skin patch instead of a traditional injection.
Zosano Pharma, Inc. www.zosanopharma.com	Macroflux® transdermal microprojection delivery system for therapeutic peptides, proteins, small molecules and vaccines
Medical Device	
Crospon www.crospon.com	With HP, developed a drug delivery patch utilizing inkjet technology.
Isis Biopolymer www.isisbiopolymer.com	IsisIQ™ Patch--a personalized, single-use, flexible, ultra-thin, transdermal drug delivery patch.
Johnson & Johnson www.jnj.com	Alza's IONSYS™ (fentanyl iontophoretic transdermal system) uses a virtually imperceptible low-intensity electrical field to rapidly transport fentanyl through the skin and into the bloodstream.

Finally, the following table gives companies actively seeking partners interested in licensing their transdermal drug delivery solutions.

Table 14 - Companies seeking partners for out-licensing of transdermal patch technology

Company	Technology
3M Drug Delivery Systems www.solutions.3m.com	Hollow Microstructure Transdermal System (hMTS)
Altea Therapeutics www.alteatherapeutics.com	PassPort® patch uses short bursts of focused thermal energy to create tiny channels in the surface of the skin, thus allowing proteins, peptides, carbohydrates, and small molecules to pass into the body without the use of needles.
Aveva Drug Delivery Systems (Nitto Denko) www.avevadds.com	Gel Matrix Adhesive; Crystal Reservoir Technology.
HP www.hp.com	Inkjet technology adapted for transdermal drug delivery.
Lavipharm www.lavipharma.gr	Proprietary permeation enhancer technology, reservoir technology.
Lohmann Therapie-Systeme (LTS) AG www.ltslohmann.com	Transdermal, Oral, LTS Laminates
Pantec Biosolutions AG www.pantec-biosolutions.com	P.L.E.A.S.E.® (Painless Laser Epidermal System)--novel transdermal delivery method for high molecular weight drugs. According to the company, its technology allows intraepidermal drug delivery (IEDD) of large and poorly permeating drugs, overcoming major hurdle to increased use of patch technology for delivery of drugs.
Vyteris www.vyteris.com	Proprietary active transdermal drug delivery technology ("active patch") delivers drugs through the skin using low-level electrical energy.

Transdermal patch technology offers potential to compete in a multibillion dollar market

Some of the benefits that transdermal patches are supposed to potentially bring to delivery of drugs which prove compatible with this method is lower drug dose for efficacy, increased control of dosage delivery and reduced discomfort versus say injection. Obviously what is also a goal is to mimic the sales of drugs such as fentanyl which was transformed from a $25m a year product to one which had sales of $1.16bn in 2007 (Johnson & Johnson's Duragesic). However, it has not alll been rosy for fentanyl this year, as fears surrounding safety recalls have seen sales decline by 20% so far for the first 9 months of the year. Part of the problem with fentanyl is that it is being prescribed inappropriately by some doctors in patients where it is contra-indicated.

Fentanyl patch recall on grounds of safety concerns

The other upside of developing a transdermal patch for a drug which may be coming off patent but still has strong sales potential is that the presentation of the drug as a patch offers product lifecycle extension.

It would be advisable for companies developing products in this area to develop strong marketing campaigns which will combat a likely growing scepticism of transdermally delivered medications in light of what is being experienced with fentanyl. Strong clinical data proving long term safety via this drug delivery route would seem to be even more important than it already is. The rewards are a multibillion dollar market which is currently, according to companies operating in the market, growing at around 11% a year, compared to average pharma industry growth in the low single digits.

Companies mentioned in Synopsis Oct. 2009

3M Drug Delivery Systems
Abeille Pharmaceuticals
Altea Therapeutics
Aveva Drug Delivery Systems
CSL Ltd.
Durect
Endo Pharmaceuticals
Ferring Pharmaceuticals
GE Healthcare
GlaxoSmithKline Biologicals
HP
Johnson & Johnson
MedImmune
Mindray
Novartis
NuPathe
Pantec
Phillips
Sanofi Pasteur
Siemens
Teikoku Pharma USA
TransPharma
UCB
Vyteris
Wyeth
Zosano Pharma

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