Confederation of Indian Industry

The Make in India Imperative – Position Paper on Regulatory and Policy Changes required for Sustained Competitiveness of the Indian Vaccine Industry

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India—the Vaccine Epicenter for Developing Economies

1. Overview of the Indian Vaccine Industry

Vaccines play a very vital role in the global public health context and provide governments and populations an economically justifiable possibility of avoiding preventable deaths and keeping debilitating and dreadful infectious diseases at bay. According to the WHO, since the introduction of WHO's Expanded Programme of Immunization in the 1980s, about 3 million lives have been saved each year and 750,000 children have been saved from disability.

The Indian vaccine industry has been instrumental in facilitating cost effective vaccination in India and also supplying vaccines to majority of the developing and underdeveloped world. [1]The industry grew to approximately $ 1 Bn in 2015 with a robust CAGR of 25% between 2011 and 2015.

Figure 1: Growth Trends in Indian Vaccine Industry, 2011-2015

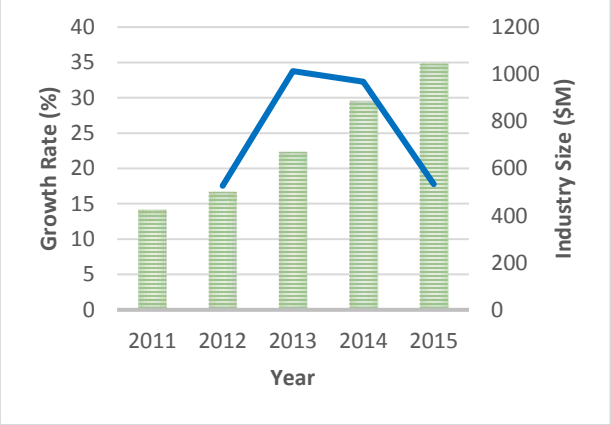
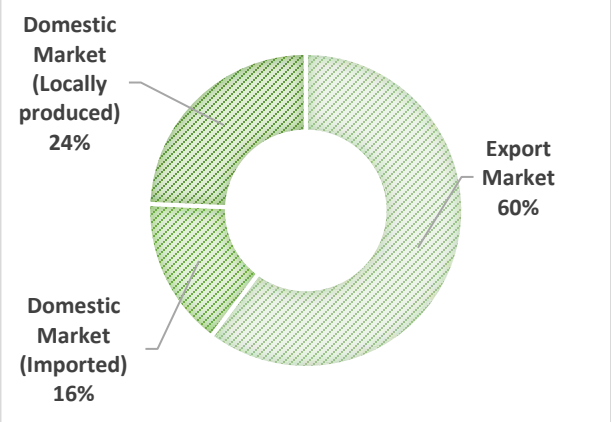


Figure 2: Segmentation of the Indian vaccine industry



Competitive Landscape

Given the high technical barrier to entry and capex requirement, the Indian vaccine industry is well consolidated with a few key players accounting for a significant bulk of the market revenue. Serum Institute of India, Biological E, Panacea Biotec, Bharat Biotec, Shantha Biotechnics (acquired by Sanofi in 2009) and Indian Immunologicals Ltd are dominant domestic manufacturers and Pfizer, MSD and Sanofi are multinationals with presence in the market. The segment has more recently gained attention from large pharmaceutical companies in India. While Zydus Cadila has also made significant investments in the segment, few other pharma companies import and market vaccines in private segment. Additionally, emerging players include younger ventures like Tergene

[1] Source: IMS Data, Capital Line, Sathguru internal estimates

Biotech developing the Pneumococcal Conjugate Vaccine (PCV) that is now a joint venture effort with Aurobindo Pharma.

2. Vaccines—A "Make in India" Success Story

India is not only the pharmacy of the world, it is also the **vaccine epicenter of the developing world**. The vaccine industry exemplifies the spirt of the 'Make-in-India' Programme and stands on a strong pedestal of domestic manufacturing success. Besides being a global vaccine manufacturing hub, vaccines is also one of the few sectors where India has historically enjoyed domestic self-sufficiency. The bulk of the Universal Immunization Program (UIP), the country's public immunization program, is supplied by Indian made vaccines. **The vaccine industry has time and again, broken affordability barriers, addressed technology challenges and has earned India the recognition of having the largest global capacity for WHO prequalified vaccine manufacturing.**

2.1. Breaking Affordability Barriers

Allaying the threat of preventable deaths, vaccines are one of the most important arsenal for public health. However, novel vaccines are often controlled by couple of product developers who command significant price premiums. This cuts out majority of the world's population and the public health imperative is unmet. Breaking this affordability barrier for India as well as rest of the world has been the most important driver of success for Indian vaccine industry. While Indian vaccine industry is replete with success stories on breaking affordability barrier with domestic technology development and manufacturing, we highlight below an indicative case of Hepatitis B, the first recombinant vaccine to be approved in India.

Hepatitis-B—A Case Study

In the late 1980s the price for a single dose of Hep-B vaccine was as high as $23 a dose and it was available only from GSK. Shantha Biotech and subsequently Bharat Biotech launched the Hep-B vaccine in 1997 at about $1 a dose. This steep price drop placed this vaccine within the reach of a number of lower and middle income households and a total of >22Mn doses were sold in the subsequent year, even when this vaccine was not a part of the Universal Immunization program. Hep-B vaccine is now included in the UIP as a four-dose regimen to infants.

A glaring case today calling for the same accomplishment is the PCV vaccine. Currently priced at more than Rs. 3,500 a dose in the private market, the 3 dose regimen costing more than Rs. 10,000 per infant for the PCV vaccine alone is unaffordable to majority of the Indian population. Other high value vaccines such as HPV carry the same affordability barrier and need priority attention from across stakeholders – industry, policymakers and regulators.

Catching up with Technology

Manufacturing expertise backed by strong technical knowhow is another cornerstone for India's success in the global vaccines market. From the Hepatitis B, the first recombinant vaccine, Indian companies have progressed to conjugated products like HiB vaccine (Haemophilus influenzae type B) and typhoid conjugate vaccine. About 6 Indian manufacturers have now successfully incorporated HiB vaccine in the pentavalent vaccine for global markets. **In fact, Indian manufacturers accounted for 20% of global supply of pentavalent vaccine in 2014.**

Continued focus on innovation has also propelled Indian manufacturers to the threshold of developing PCV and HPV, 2 key vaccines which offers untapped potential in the currently MNC dominated GAVI supply. Four Indian companies currently have pre-clinical and clinical candidates for PCV including Serum Institute of India, Panacea Biotec, Biological E and Tergene Biotech. Focus on strong technology foundation has been the key enabler for success of the Indian vaccine industry and we would like to highlight the criticality of ensuring this strength is intensified in an appropriately rewarding ecosystem.

2.2. Vaccinating the World

While we earlier pointed to Indian vaccine industry's success in exports, the real laurel in the export success rests in the markets served and the consequent public health impact. Global Alliance for Vaccines and Immunization (GAVI), is an international non-profit organization formed in the year 2000 with the aim of improving access and affordability of essential vaccines to about 73 low and middle income countries of the world. It works through public-private partnership and vaccines for GAVI supply are negotiated through UNICEF.

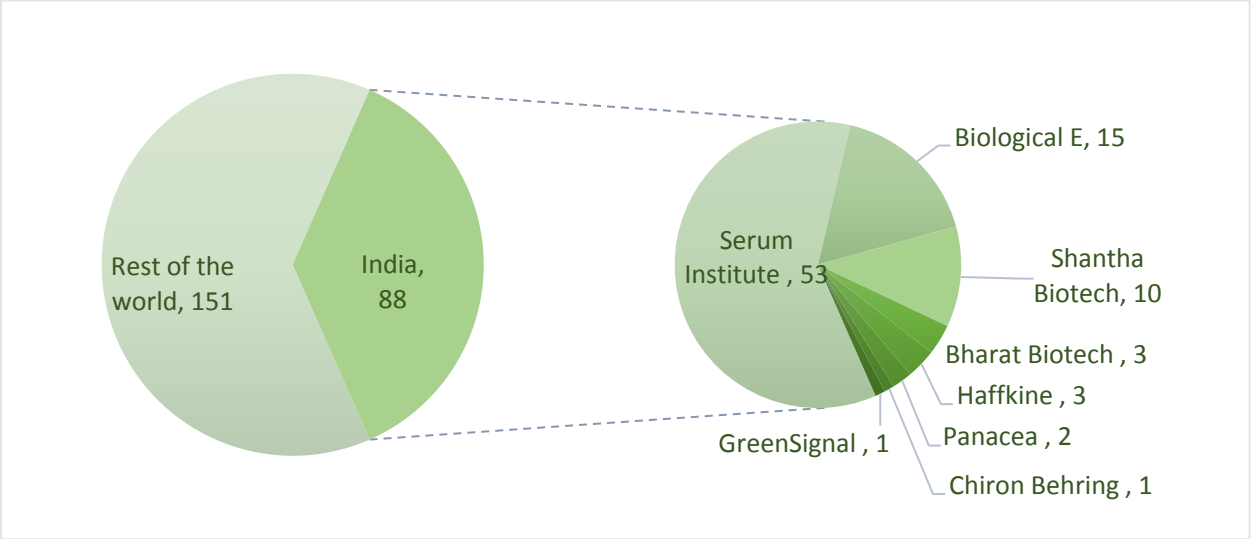
Today, India remains unmatched in its price competitiveness to GAVI and has established itself as a top supplier with commendable penetration success. **According to GAVI data, India accounted for a dominant 60% of their vaccine volume supply in 2014**. The following table summarizes the specifics.

Figure 3: Indian Industry Participation in GAVI Supply

Type of Vaccine	UNICEF Total Volume (doses)	Volume Supply from India (doses)	Countries covered	GAVI Volume Supply from India (%)
Meningococcal A (men A) conjugate vaccines	~70 million	~70 million	15	100%
Measles-Rubella (MR)	~127 million	~127 million		100%
Measles Vaccine	~ 180 million	> 144 million	14	>80%
Pentavalent Vaccine	~180 million	> 144 million	78	>80%

[2]Analyzing WHO pre-qualified (PQed) vaccines[3], we note that 37% (89 products) of the total 240 vaccine products approved are from Indian manufacturers, highest share from any single country. Serum Institute of India is globally the largest manufacturer of WHO PQed vaccines, with 54 products. 7 other manufacturers account for the remaining share.

Figure 4: Number of WHO PQed Products, Global



The sheer volume of vaccine supplies highlighted in the table above are testament to the reputation built by Indian vaccine industry as a reliable and cost effective supplier of complex products at a scale that meets global demand. The below case of Meningitis is a classic success story of India vaccinating the world.

Meningitis—a Case Study

The meningitis vaccine was available in India only from 3 MNCs viz. GSK, Sanofi Aventis & Wyeth (now Pfizer) at prices ranging from INR 800 to INR 1200 a dose. In 2007, an Indian company, Serum Institute of India launched it at less than half the price at INR 375 a dose, which led to an increase in usage of the vaccine in country. As of 2014, this highly effective vaccine costs ~$0.6 a dose at GAVI procurement price and used in nearly 100Mn doses in the countries of African meningitis belt.

[2] Source: GAVI, UNICEF
[3] Source: WHO Immunization standards

Given the affordability element introduced by Indian manufacturers when they enter global public supplies, they expand markets and public health reach but enjoy a lower market share by value. Thus, though India accounted for 60% of volume supply to GAVI in 2014, in value terms this translated to only 30% contribution. This large gap is created mainly by 2 vaccines—the pneumococcal conjugate vaccine (PCV) and the human papilloma virus (HPV) vaccine, for which there are currently no Indian manufacturers and entire global supply, including Indian domestic market supply is dominated by two multinationals manufacturing in high cost countries. PCV, for instance, accounts for 39% in value but only 3% in volume of all UNICEF's vaccine procurement. And this skewed value concentration was despite about a billion doses of PCV demand forecast remaining uncommitted for GAVI. Robust pipeline engagement by Indian industry in PCV and HPV indicates potential to gain substantial share of these products as well in the future. This global public health urgency and Indian industry's potential to expand access to these important vaccines across LMIC highlights the importance of regulatory changes requested to ensure elimination of redundancies and acceleration of path to market for vaccines produced by Indian companies.

3. Immunization in India

3.1. The Universal Immunization Programme (UIP)

Approximately 80% of India's domestic demand for vaccines is addressed by the UIP and is provided free of cost to the beneficiaries by the government. According to the WHO data, the government expenditure on routine immunization was about $ 101 million in 2014. The UIP portfolio, built on recommendations from the WHO, covered 7 vaccines until 2015, with the pentavalent vaccine being the most recent addition in selected states. The current political environment in India places huge emphasis on improving vaccine access and in 2014, 4 more vaccines were added to the UIP, namely rotavirus, rubella (as MR vaccine), adult Japanese Encephalitis (JE) vaccine in districts with high incidence levels, and the injectable polio vaccine (IPV). The government has also announced priority adoption of PCV and HPV vaccines in the near future, as part of the India Newborn Action Plan (INAP) launched in 2014. This is undoubtedly the need of the hour as India accounts for a considerable share in the global burden for both these diseases.

Indian UIP has been supported by GAVI since 2002. India begins its transition towards self-financing its vaccine program from 2017 and GAVI has recently announced funding support of $ 500 M for the period 2017-2020 after which India will completely graduate out from GAVI support.

3.2. Private Vaccination

Private vaccination in India remains a small sector with respect to volume coverage, accounting for a small 20% share. However, it remains an important channel for some key vaccines which have managed to generate reasonable revenues through the private channel. Some of the key private market vaccines are PCV, Hepatitis A, Varicella, Rabies and Influenza (together with revenues of Rs. 850 crores in 2015).

Although the private vaccination market is growing in line with raising middle class affordability, key life-saving vaccines such as PCV, which is today a 100% private market, remains a luxury enjoyed only by a privileged few. This is ironic, as the high mortality rates for pneumonia is strongly linked to poverty-related factors such as under-nutrition, unsanitary living conditions and lack of access to hygienic water, and this target population remains largely uncovered by PCV vaccination today. Although the Indian PCV vaccines market is worth 400 crores, highest among private vaccines, volume contribution to revenue remains low at a meagre coverage of 1.7%.

Figure 5: Coverage of PCV, 2015

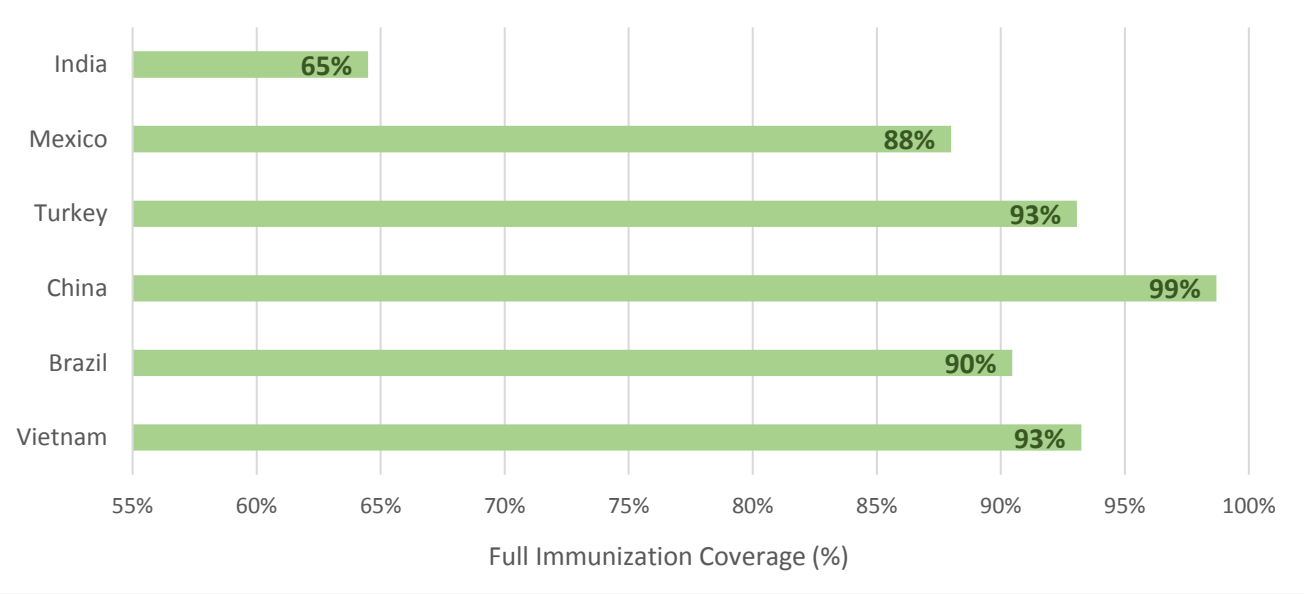
Market Size (INR)	Price per dose (INR)	Total Volumes (No of doses)	Number of Children Covered	Coverage %
~ 400 crores	~ 3,500	1.1 million	380,952*	1.5%

[4]*Assuming entire sales pertain to pediatric vaccines

3.3. Immunization Coverage in India

India lags behind its global peers when it comes to full immunization coverage (FIC), as seen in the chart below as per WHO published statistics. Mexico and Brazil's portfolio is far superior to that of India and China, as it includes both HPV and PCV. Considering India's portfolio is more in line with China's, this disparity between the two countries is of definite concern.

Figure 6: Full Immunization Coverage (%) of Select Countries, 2015



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This clearly indicated that improving vaccine coverage in India is the need of the hour and pertinent government measures are already underway, with Mission Indradhanush targeting 90% coverage by 2020.

[4] Source: IMS data, Sathguru internal estimates

[5] Source: *Indian coverage data from ITSU referenced against WHO data for other countries.*

3.4. Progressing Towards a Robust Tomorrow

3.4.1. Indian Healthcare and Immunization Expenditure

In order to identify the key facilitators for future growth opportunities for the Indian vaccines industry, we take a comparative look at the spending patterns of a few aspirational middle income countries comparable to India in size and economic development. [6]

Figure 7: Total Govt. Spend on Healthcare, By Country, 2014

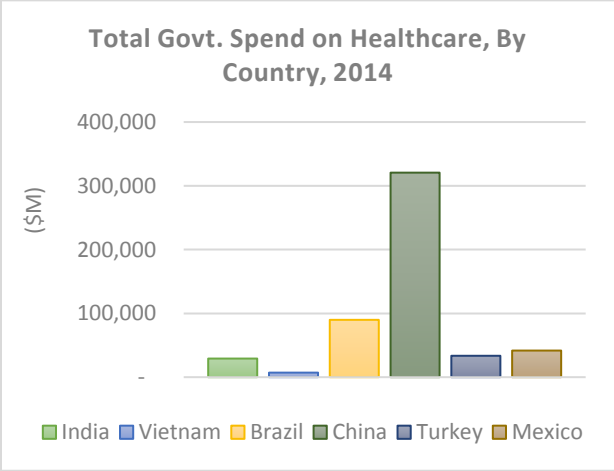


Figure 8: Per Capita Govt. Spend on Healthcare, By Country, 2014

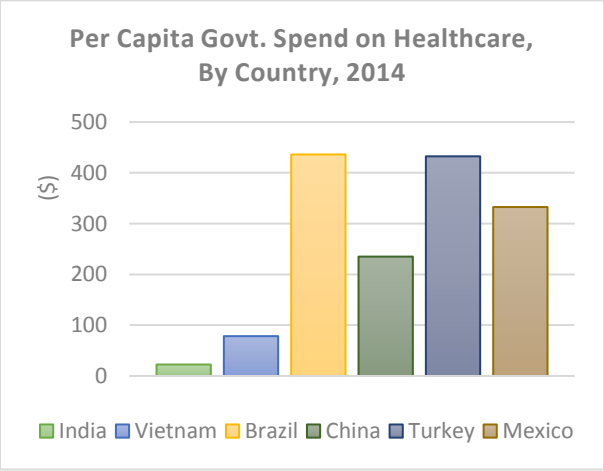
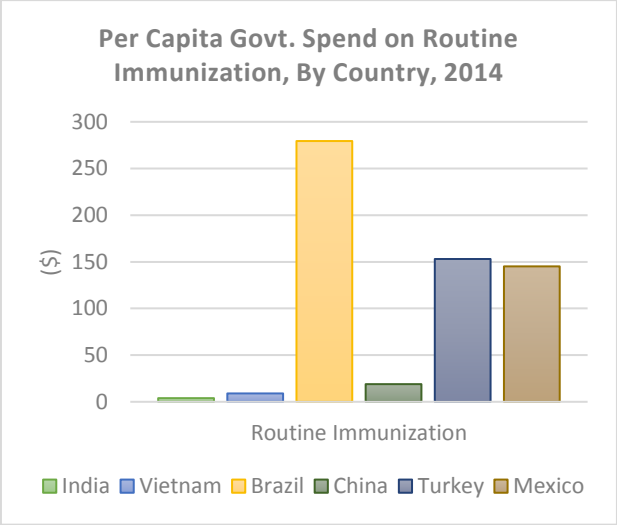


Figure 9: Per Capita Govt. Spend on Routine Immunization, By Country, 2014



While China spends the highest on healthcare and Vietnam the lowest, Brazil and Turkey take lead in per capita spending on healthcare. India fares the lowest among all emerging markets in terms of per capita healthcare expenditure, lower than even Vietnam whose total healthcare expenditure is lower than India.

Another key parameter of high significance to the vaccines industry is government expenditure on routine immunizations which is a key element to help minimize overall burden on the economy's healthcare system.

Despite government accounting for 80% share in routine immunization expenditure in India, the per capita spend by government is observed to be lowest in India at approximately $ 4. Brazil, Mexico, and Turkey have PCV

[6] Source: WHO data

administration as part of its National Immunization Program, thus accounting for the high per capita spend. Brazil and Mexico also has some structured HPV vaccination programs at either the national or sub-national levels since 2011. It is sad to note that even Vietnam, the only country in this list to have a lower share of government finance for immunization, has a higher per capita expenditure than India.

3.4.2. Moving towards an ideal vaccine portfolio

An ideal vaccine portfolio is the cornerstone of initiatives to accomplish any country's public health goals. Although favorable political environment has brought immunization into focus in recent years in India, gaps still exist when compared to vaccine portfolio of developed countries and even IAP recommendations. An active process should be adopted to periodically evaluate new additions to the UIP portfolio.

Figure 10: A Comparison of Different Vaccine Schedules

Vaccine Category	US Vaccines for Children (VFC) program	India's Universal Immunization Program (UIP)	IAP Recommended vaccines
BCG	🔴	🟢	🔵
DPT	🟢	🟢	🔵
MR	🔴	🟡	🔴
MMR	🟢	🔴	🔵
HiB	🟢	🟡	🔵
HepA	🟢	🔴	🔵
HepB	🟢	🟢	🔵
OPV	🔴	🟢	🔵
IPV	🟢	🟡	🔵
Rotavirus	🟢	🟡	🔵
PCV	🟢	🟠	🔵
HPV	🟢	🟠	🔵
Men A	🟢	🔴	🟣
Varicella	🟢	🔴	🔵
Influenza	🟢	🔴	🟣
Typhoid conjugate	🔴	🔴	🔵

Key: 🟢 **Covered;** 🟡 **Recently Included;** 🟠 **Planned to be covered;** 🔵 **Recommended** 🔴 **Uncovered/ Not Recommended** 🟣 **Recommended in special cases;**

PCV and HPV Adoptions: Although announced as next near term additions to the UIP, there are challenges to be addressed before the vision can be actualized. There are currently no Indian manufacturers but there are four Indian companies developing the vaccine today. However, the pace of development of these products have been so far

hindered by bureaucratic red tape and delays in license and approvals. Such challenges, besides costing Indian manufacturers, also stand in the way of PCV roll-out in UIP.

In order to be able to add PCV to the UIP portfolio, the current government spend on immunization needs to be increased by 2 fold.

While PCV is announced to be adopted in 2017-18 timeline, no confirmed timelines have been announced for HPV yet and India lacks in adequate HPV pipeline today. Funding needs to be accelerated in order to build a more robust HPV pipeline for the country in order to be able to add it to the UIP in near term.

Other Available Vaccines for Near Term Adoption: Apart from these, there are also other critical diseases, which needs attention in a tropical country such as India and for which vaccines are available. These include Typhoid, Cholera and Hepatitis E.

Other Pipeline Vaccines for Long term Adoptions: Other crucial diseases for which India needs to foster development for more effective next generation vaccines include Tuberculosis, Dengue, Malaria, Chickungunya.

Looking forward to 2020: Considering so many eligible candidates exist for UIP inclusion, two possible scenarios are considered, depending on initiatives taken. PCV is already announced to be included and thus the base case scenario considers inclusion of one additional vaccine, possibly HPV while the optimistic scenario considers inclusion of two additional vaccines. The below table summarizes the corresponding requirement in terms of government spend, above and beyond GAVI's allocated funds.

[7]

Figure 11: 2020 UIP Scenarios

	Base case Scenario	**Optimistic Scenario**
Additional Vaccines covered in UIP	PCV+ 1 additional vaccine	PCV + 2 additional vaccines
Forecasted Indian public vaccines market, 2020	~ $ 500 Mn	~ $ 600 Mn
Government Spend on Vaccines, 2014	$ 89 Mn	$ 89 Mn
Required Increase in Government Spend by 2020 (%)	**~ 300%**	**~ 400%**
Note: Spend calculated based on current lowest GAVI prices.		

In order to actualize the set immunization goals in the near term, in the base case scenario, the government spend on immunization needs to be increased 3 fold.

[7] Source: Sathguru internal estimates

3.4.3. Strengthening Health Systems

Strengthening of health systems is another key element to be addressed for accomplishing future immunization goals. India is already embarked on an effort to improve vaccination coverage with Mission 'Indradhanush' which aims to intensify routine immunization in 200 low-coverage districts to achieve more than 90% coverage by 2020; and strengthening of health systems is an absolute pre-requisite to actualize this vision. We would also like to emphasize on criticality of education and awareness creation efforts to address demand side issues in India's diverse and complex socio-economic milieu.

Cold chain infrastructure: Lack of required cold chain infrastructure is a key limiting factor in India today.

Although the rotavirus vaccine is approved in India and got included in the UIP in 2014, actual implementation is lagging due to lack of the necessary cold chain infrastructure.

According to data from the National Cold Chain Assessment done in 2014 by the National Cold Chain & Vaccine Management Resource Centre (NCCVMRC), there already exists a 25% shortage in overall cold chain capacity to meet the current UIP needs. Our analysis of the capacity at various points of the cold chain indicates that the shortages are more glaring at the primary leg of the cold chain—about 200-300% in walk-in coolers (WIC) and walk-in freezers (WIF).

While these infrastructure gaps pertain to just the current UIP, it gets further amplified by the already announced inclusions of IPV and rota vaccines and the planned inclusion of PCV in the near term. Thus, rapid strengthening of cold chain infrastructure is quintessential to achieve the near term immunization goals of the nation.

Enabling Indian Industry to Address this Future Need

Enabling Indian industry to address this future need

India is at the cusp of a new era in vaccines as we graduate from GAVI support and begin self-financing our immunization program in the near future. We also stand at the threshold where the country is committed to address critical gaps in our UIP portfolio such as PCV and HPV. While the Government's commitment to bridge this gap and expand vaccination coverage is very encouraging, we need to take cognizance of the economic implication with cost of vaccination increasing three fold. We have to note that these are not the last vaccine challenges to conquer. Future vaccines are bound to be as complex or more. As a country we need to ensure immunization is a priority and we have sustainable capacity to efficiently respond to public health threats with possible vaccination programs in a time sensitive and cost effective manner.

Thus, it is highly imperative at this point to understand what facilitators are needed to enable our country to accomplish these goals. These building blocks will also be important for the industry to build on this foundation of success and continue to break affordability barriers and supply required vaccines volumes for India and the world. The issues involved are complex and cover different aspects of vaccine manufacturing and marketing. Based on industry inputs and feedback, we have summarized some of the key policy and regulatory related recommendations required for an enabling ecosystem and environment:

1. Policy Related Recommendations

A. Fiscal and Funding Support

I. Quantum leap in level of soft funding support for product development

Challenge

India today has a good foundation of seed funding mechanisms such as Biotechnology Industry Partnership Programme (BIPP) and Biotechnology Ignition Grant (BIG) from Biotechnology Industry Research Assistance Council (BIRAC) and Technology Development Board from DST. A new venture commencing technology efforts is no more constrained by lack of seed capital. However, scale-up capital and funding support of substantial quantum is still lacking.

Implication

In the vaccine segment, product development investments are significant, lead time is long and risk is high. India has to shoulder significant binary risk investments in a market where monetization is largely linked to public health adoption and procurement contracts. Current challenges such as PCV and HPV being tackled by the industry are both technically complex and are of highest public health criticality. These are vaccines where India and rest of the developing world are completely dependent on exorbitantly priced imports from multinationals manufacturing in high cost countries. Even beyond these two challenges, the vaccine industry needs to continuously engage in product development to remain competitive. Globally, substantial grants are available even for scale-up funding, clinical validation and infrastructure creation, especially in the EU, USA as as well as Asian countries such as Korea. Indian companies are increasingly competing with competitors from other countries who have benefited from such scale-up funding support and dearth of such options in India impacts competitiveness of Indian industry.

Recommendation

The Indian vaccine industry should be supported by appropriately large national funding programs with structured funding pathways for nationally critical vaccines. In addition to being substantial in quantum, the funding program should consider context of vaccine technology development and provide technology access funding.

II. Provide Globally Comparable Fiscal Incentives

Challenge

The special 'royalty tax' which was introduced in the 2016 budget provides tax rebates on royalty income earned from out-licensing technologies. The discounted royalty tax is 10% against the standard rate of 30% after deducting expenses. While this rebate is definitely a positive step towards incentivizing indigenous innovation, this was accompanied by a lower tax benefit on overall in-house R&D expenditure. The tax deductions of 200% offered on in-house R&D expenditure was reduced to 150% for 2017-2020 and 100% thereafter.

Implication

The decrease in tax benefit on in-house R&D expenditure is very discouraging, especially in a segment like vaccines, where the industry is aspiring to build global competitiveness based on technology strength. Many countries across the globe provide more favorable tax incentives for R&D. Indicative global references[8] are outlined below.

Singapore: A base level of 100% deduction is given which is followed by additional 50%. Additionally, a 250% (for Singapore-based R&D) or 300% (for non-Singapore-based R&D) enhanced deduction is given

Malaysia: 200 % super deduction is given. In addition an Investment tax allowance of 100 % on qualified capital expense for R &D Services. The above incentive applies to R&D conducted outside Malaysia as well.

UK: There is the Patent Box Scheme wherein discoveries and innovations are being imposed preferential tax.

Ireland: Besides having one of the lowest corporate tax rates of 12.5%, a 25% volume based credit is given on the expenditure on infrastructure, with the option of carrying forward unused credits indefinitely to reduce any preceding tax liability. IP Tool Box scheme also provides incentives for innovations in products and processes.

Switzerland: 130% tax exemption on R&D expenditure for large companies and 230% for SMEs

Recommendation

When benchmarked with global ecosystems that are encouraging greater biopharmaceutical R&D engagement, our fiscal incentives fall behind. Industry feedback calls for globally comparable fiscal incentives as well as strategic initiatives such a patent box that will encourage greater investments in product development.

[8] Source: Deloitte 2015 Global Survey of R&D Incentives, KPMG Tax Incentives for R&D in Switzerland-2016

B. Avoid Misconstrued Inclusion of Vaccines in NLEM

Challenge

The National List of Essential Medicines (NLEM) 2011 included certain specific vaccines (BCG, DPT, Hepatitis B, Measles, OPV, Rabies Vaccine, Tetanus Toxoid) and the NLEM-2015 broadened inclusion to any vaccine listed in the UIP.

Implication

While such inclusion is with the fair intent of providing access to all, it is seen as a redundant step that only serves to demotivate the industry. Vaccines meet the key principle of 'essentiality' as laid down in the National Pharmaceutical Pricing Policy-2012 (NPPP). However, the core objective of the NPPP of 'ensuing availability of required medicines at reasonable prices' doesn't apply to vaccines given a specific program for universal vaccination, the UIP[9]. India's UIP is one of the largest of its kind in the world, in terms of quantity of vaccine used, as well as number of beneficiaries reached out to. It caters to nearly 27 million infants and 30 million pregnant women annually free of cost. Vaccines procured by the public sector at UIP tendered prices are very nominal and comparable with the lowest public health procurement prices globally and these are provided to the Indian population free of cost. Hence, placing vaccines in the NLEM is a redundant step that does not expand healthcare access but only threatens to extend price controls to the limited private market that exists and demotivate industry in a high capex segment.

Recommendation

Given structured public health programs in place such as UIP and Mission Indradhanush, any concerns around access to vaccines at affordable prices are laid to rest as the country's infants are vaccinated for free. Thus, placing vaccines under NLEM on retail trade is not meaningful. Industry feedback points to this anomaly and requests for reconsideration of misconstrued inclusion of UIP vaccines in the NLEM.

[9] Immunization Technical Support Unit

C. Increase government spend on immunization

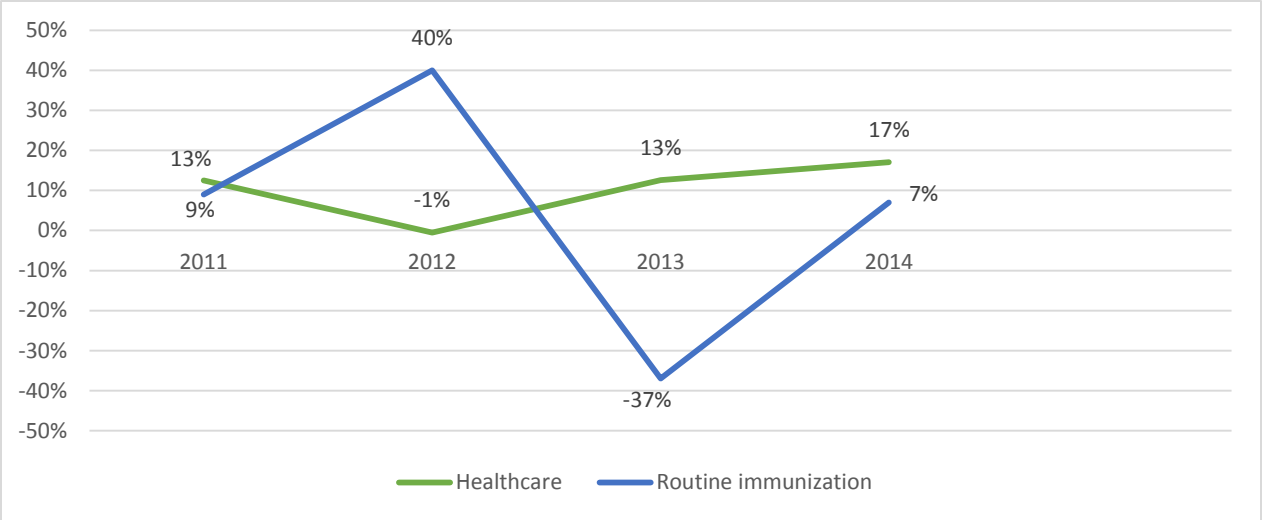
Challenge

Although healthcare budgets have consistently seen double digit growth (except in 2012), the growth in immunization expenditure calls for attention. In fact, immunization expenditure as a percentage of healthcare expenditure has been on a downward swing.

Implication

Government spend on immunization is a key foundational element for health in the country and industry feedback indicates that this spend is sub-optimal in India. This fact is evident from the below chart indicating healthcare and immunization expenditure over the past few years.

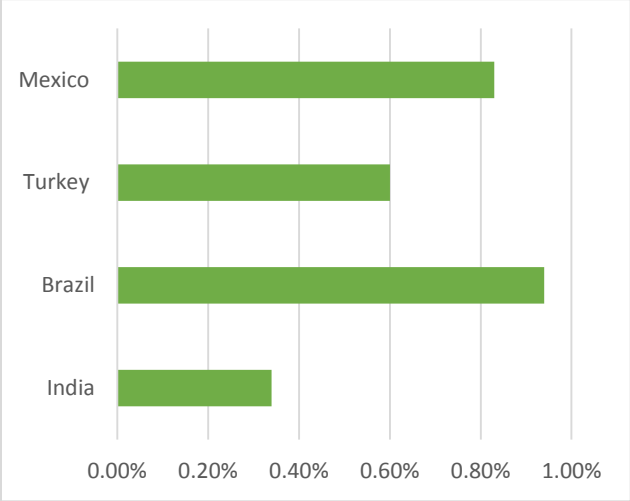
Figure 9: YOY Growth in Government Expenditure[10]



Further data from WHO indicates that India is amongst the lowest in terms of immunization expenditure as a percentage of healthcare expenditure when compared to other comparable middle income countries.

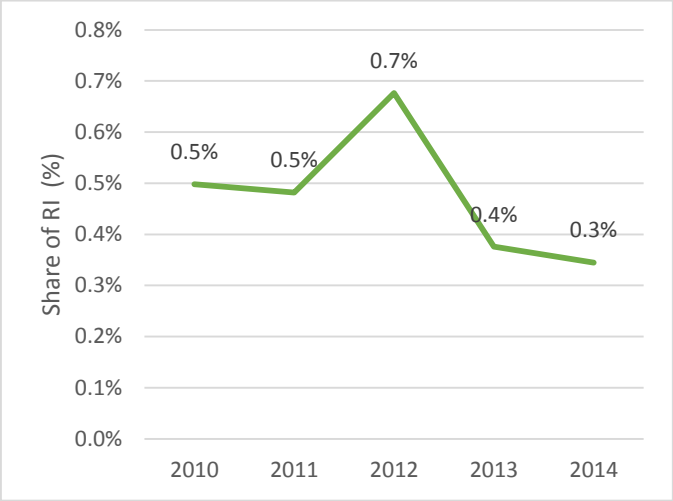
[10] Source: WHO data

Figure 10: Routine Immunization as a % of Govt. Healthcare Expenditure, 2014



[11]

Figure 11: Trends in Routine Immunization as a % of Govt. Healthcare Expenditure, India



Additionally, in India vaccines are not covered under most private health insurance programs in India. In fact, some insurance schemes even explicitly mention them as permanent exclusions. Mission Indradhanush is a commendable effort and the Government's intent to improve UIP portfolio and coverage rates of different vaccines are recognized. However, the expenditure on immunization is still a point of concern and calls for attention, as the near term product adoptions can lead to 3X increase in vaccination spending itself. The industry urges the Government to make vaccines a national priority and address the issue of under-funding for vaccines.

Recommendation

It is important that the Government continues to prioritize vaccines and implements planned introductions without delays and actively pursues an ideal and robust immunization program. We would like to emphasize the criticality of immunization as a means to achieve the MDG Goals and draw attention to the need for increased spending on immunization. Additionally, the industry also pushes for further strengthening of health systems and consideration of mandatory covering of vaccines under health insurance reimbursements and ESI.

[11] Source: WHO data

D. Address current regulatory challenges

Challenge

Regulatory pathway for vaccines is currently laden with delays and redundancies. All vaccines are classified as new drugs even if they are follow-on products to currently approved vaccines. There are multiple agencies involved in the regulatory process and the overall timeline for product approval is much stretched. Defined timelines are lacking for most critical steps of the regulatory process and there is high level of ambiguity on anticipated timelines at every step.

Implication

Redundant requirements and capacity gaps cause hardship for industry and result in a cumbersome process. The unduly long time product approval timelines make the industry uncompetitive and directly impede industry growth. As critical public health products, significant delays in product launch also impact affordable procurement possibilities for the Indian Government and global public health agencies and delay availability of vaccines. There is an urgent need to address the regulatory challenges and create an efficient regulatory framework for vaccine approval.

Recommendations

- Regulatory challenges are described in greater detail in the next section. To ensure sustained competitiveness of the Indian industry and timely response to public health needs, these regulatory challenges need to be addressed on a priority basis to create an efficient regulatory pathway that is comparable to global benchmarks.

2. Regulatory Recommendations

A. Eliminate redundancy in licensing processes

The vaccine industry is currently straddled with several levels of redundancies and delay-causing steps in the regulatory process. There is great need to review the regulatory process and eliminate these to ensure the process is efficient. Indicative redundancies with high hardship to industry and need immediate attention and remedial action are highlighted below:

I. Repetitive need for Test License (Form 29) to produce material for R&D and clinical trials

Challenge

The industry deals with the challenge of need for Form 29 licensing at multiple stages of product development and product approval. As per Rule 33 and rule 34 of Drugs & Cosmetics Act 1940 and Rules 1945, Test License (Form 29) needs to be obtained to produce material for R&D and clinical trials. Currently, all sites including those that are already inspected by CDSCO and approved for cGMP manufacturing need to be inspected again by CDSCO along with CDL and State Licensing Authority as part of this process for form 29 NOC for producing material.

This requirement entails a long, complex and time consuming regulatory pathway involving CDSCO (DCGI), Zonal CDSCO office and State Licensing Authority. No such requirement exists in even in US or EU and licensure is normally required only for product registration or GMP accreditation. Such a requirement does not even exist for pharmaceuticals in India.

Implication

Information provided by 5 Indian manufacturers indicates that on an average, the timeline from request for inspection to issue of Form 29 was around 6 months. Redundant licensing requirement (Form 29) results in significant delays in final launch of products under development, thereby resulting in significant financial loss for the industry as well as public health hardship given the critical public health need for the vaccines produced across India and other LMIC.

Additionally, pharmacovigilance inspections in clinical trial sites are currently done by personnel drug inspectors or junior microbiology professors who do not always have the pertinent subject matter knowledge.

Recommendation

- The industry recommends elimination of requirement of NOC and test license. At the minimum, facilities that are already approved for cGMP manufacturing should not be re-inspected for granting test license for new product and every subsequent product should be granted NOC followed by test license without joint inspection
- The industry also recommends that approval of new sites for vaccines be delegated to zonal CDSCO offices, as is currently in the case of other pharmaceuticals, in order to further accelerate processing
- The industry calls for deployment of well-qualified subject experts for different types of inspections

II. Joint Site Inspections

Challenge

In addition to an unreasonably high number of Form 29 inspections, the industry also deals with the bane of joint site inspections. Joint site inspections are required for different approvals viz. NOC for test license, marketing authorization, post approval change approval and certifications for GMP, WHO GMP certificate etc. The joint site inspections again are specific to vaccine industry and no such requirement exists anywhere in the world or even for pharmaceutical companies in India. Joint site inspections are a practical challenge and always result in undue delays given the paucity of experts and constraints on their time.

Implication

Joint site inspections further compound the problem of delays on account of a high number of inspections required as per the Indian regulatory requirements for vaccines.

Given paucity of experts, on an average, companies have waited for 4-6 months for joint inspections from the time of application. This is compounded by the number of joint site inspections required, which is about 7 inspections per year on an average, based on data provided by 5 Indian manufacturers. Thus, on an average companies stand to bear delay of about 30 months and this results in significant national and international public health hardship and loss of revenue for companies. As the manufacturing license is issued after careful evaluation of application and joint site inspection as per the GMP requirements, the industry views the additional site inspection for subsequent approvals or licenses (NOC for test license, marketing authorization, post approval change approval and certificates for GMP, and WHO GMP) as redundant.

Recommendation

- The industry recommends that the requirement for joint inspections be retained only for product registration/GMP accreditation, in par with global standards, and calls for elimination of need for joint site inspections for every step of the vaccine produce development and approval process.
- Every site is subject to an annual risk based inspection by CDSCO and state licensing authority, which is suggested to serve as the basis for grant of GMP / subsequent WHO GMP certificates
- The industry also recommends extending validity of WHOGMP certificate to 5 years.

III. Need for defined timelines for various steps of the approval process

Challenge

Vaccines, in India, go through three / four tier review procedures through RCGM, CDSCO, SEC, TC and sometimes APEX / IND committees. With such elaborate review procedures, it takes anywhere from 4-8 years for the product to be commercialized, and much longer for novel vaccines. These stretched timelines call for urgent consideration of defined time limits for every step of the review process and an efficient regulatory pathway that is comparable to global benchmarks.

Globally, most advanced regulatory frameworks have specified time stipulations that obligate regulators to respond within a defined period and provide alternatives for industry if this is not met. We have highlighted below indicatives timelines from USFDA:

Indicative timelines - USFDA

- **Clinical Trial NOC:** If no response is obtained within 30 days, clinical trials can be initiated.
- **Marketing Authorization Application:** Comments are sent within 60 days, stating the approval or rejection status of the application.

Implications

In the absence of defined time limits for all regulatory processes, time taken for various steps such as clinical trial NOCs and marketing authorization approvals are hard to estimate and are often subject to undue delays. This again leads to frustration in regulatory process, stretched product launch timelines and loss of competitiveness in the global landscape.

Recommendations

- Industry recommends that 3-4 tier review procedure be replaced with a single expert approval committee to enable better control on timelines.
- Industry calls for defined timelines for various regulatory steps, emphasis on defined timelines being adhered to and efficiency in the regulatory pathway

B. Accelerate Clinical Pathway

Steer away from new drug pathway to more pragmatic requirements for follow-on vaccines

Challenge

Currently, all vaccines developed in India are considered as new drugs and need to go through a comprehensive pre-clinical and phase I to phase III clinical trial pathway. The regulatory requirements do not take cognizance of vaccines being modifications of existing formulations or being follow-on products and apply the same requirement for all products seeking approval in India. Additionally, issuance of clinical trial NOC goes through a multi-window review and approval process by RCGM / CDSCO / SEC / TC / APEX / IND committees as applicable.

Implication

The blanket application of new drug pathway in India for all vaccines leads to significant hardship for industry and calls for unwarranted investment of time and financial resources in pre-clinical and clinical steps not required in the global context. Industry would like to particularly point to the case of follow-on vaccines where other companies are selling the same vaccine in India or modifications of vaccines (such as a quadrivalent formulation of an existing pentavalent vaccine). A pre-clinical evaluation or a complete Phase I to Phase III pathway are not called for in either. Such a requirement again stretches the regulatory approval timeline, delays product launch and has significant financial impact on industry and economic impact on countries given the public health importance of vaccines.

In the global landscape, concept of a “similar biological medicinal product” is also applicable for vaccines in EU as well as Japan and thus follow-on vaccines follow the biosimilar pathway in these regions. There is a pressing need to address the unwarranted requirements of following a new drug pathway for all vaccines and have a differentiated pathway for the three categories —novel vaccines, follow-on vaccines and modified versions of existing vaccines.

Recommendations

- The current requirement of following a new drug pathway should be retained for novel vaccines
- "Follow on vaccines" to be declassified from "new drugs" and follow a pathway similar to biosimilars. CDSCO should be empowered to issue clinical trial NOC on its own without involvement from other committees.
- Modified versions—Vaccines and/or components of vaccines that are already licensed should only require bridging studies and not require preclinical and phase I trials. (Eg: Removal of serotypes- pentavalent to quadrivalent vaccine)

Conclusion

Conclusion

India is likely to remain the epicenter of vaccines in the developing world, for both supply and demand side reasons. While it is poised well to continue its dominant position as a vaccine manufacturing hub, it also needs to improve immunization coverage and portfolio in the country to meet its MDG goals.

India's Significance to the Vaccine Industry	India's Significance to Global Immunization Goals
✓ History of domestic self-sufficiency for UIP vaccines ✓ 60% of all GAVI vaccines have been supplied from India including 100% of MR and Men A vaccines and > 80% of Measles and Pentavalent vaccines ✓ 37% of all WHO-PQed vaccine products are of Indian origin ✓ 8 Indian companies possess one or more WHO PQed vaccine products	✓ India is the most populous GAVI eligible country, ✓ India accounts for 1/5th of child mortality worldwide ✓ India accounts for 1/4th of all unimmunized children in GAVI eligible countries ✓ Worldwide, India accounts for • ~20% of pneumococcal, rotavirus and measles deaths • ~25% of cervical cancer deaths • ~38% of the global congenital rubella syndrome (CRS)

The industry is positioned well to further build on this foundation of manufacturing success and strengthen its global impact in line with the Government's Make-in-India programme. However, to accomplish this it is important that the policy and regulatory challenges outlined earlier are addressed to ensure sustained competitiveness of the industry. Similarly, it is also encouraging to note the Government's current focus on immunization with initiatives such as Mission Indradhanush. It is also equally important to expand such focus multi-fold and prioritize immunization spending to progress towards a healthy India in an accelerated manner.

In conclusion, we would like to highlight the criticality of a concerted effort to bridge the gaps highlighted in this position paper and the need for a multi-stakeholder approach to move to the next pedestal of manufacturing and immunization success.

Abbreviations

BCG	Bacillus Calmette–Guérin vaccine		HPV	Human Papilloma Virus
BIG	Biotechnology Ignition Grant		IMR	Infant Mortality Rate
BIPP	Biotechnology Industry Partnership Programme		INAP	India Newborn Action Plan
BIRAC	Biotechnology Industry Research Assistance Council		IPV	Injectable polio vaccine
Bn	Billion		LMIC	low and middle income countries
CAGR	Compound Annual Growth Rate		Men A	Meningitis A vaccine
CDL	Central Drugs Laboratory		MMR	Measles, Mumps, and Rubella vaccine
CDSCO	Central Drugs Standard Control Organization		Mn	Million
CRS	congenital rubella syndrome		MR	measles and rubella virus vaccine
DCGI	Drug Controller General of India		NCCVMRC	National Cold Chain & Vaccine Management Resource Centre
DST	Department Of Science & Technology		NLEM	National List of Essential Medicines
DTP	Diphtheria, Tetanus toxoids and Pertussis		NOC	No objection certificate
eVIN	electronic Vaccine Intelligence Network		NPPA	National Pharmaceutical Pricing Authority
EVM	Global Effective Vaccine Management		NPPP	National Pharmaceutical Pricing Policy 2012
FIC	Full Immunization Coverage		OPV	Oral polio vaccine
GAVI	Global Alliance for Vaccines and Immunization		PATH	Program for Appropriate Technology in Health
GMO	Genetically modified organism		PCV	Pneumococcal Conjugate Vaccine
GMP	Good Manufacturing Practice		PQ	Pre-Qualified
GSK	GlaxoSmithKline		RCGM	Review Committee on Genetic Manipulation
H1N1	Influenza A virus subtype H1N1 vaccine		UIP	Universal Immunization Program
Hep A	Hepatitis A vaccine		UNICEF	United Nations International Children's Emergency Fund
Hep B	Hepatitis B vaccine		WHO	World Health Organization
HiB	Haemophilus influenzae type B vaccine		YOY	Year-on-year

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