Medicines regulation

Regulatory systems in India

An important global hub for medical products and technologies

India has emerged as a major supplier of medical products globally. In recent years, great progress has been achieved in upgrading health product regulation in India in line with internationally accepted standards. This article gives an overview of the regulatory system in India and some recent initiatives that will make regulatory operations more efficient to ensure effective control and facilitate cooperation with other agencies. There is also the link to universal health coverage, the underlying theme being access to affordable and quality medical products. The country is playing an important role in the global landscape and is called by some “the pharmacy of the world”.

Introduction

The role of a proactive Indian national regulatory authority (NRA) is important in facilitating access to good quality, safe medical products worldwide. Medical products (medicines, vaccines, diagnostic, devices) are critical for achieving the goals of the 2030 Agenda for Sustainable Development, and in particular Goal 3: “Ensure healthy lives and promote well-being for all at all ages”.

The Indian pharmaceutical industry has achieved an eminent global position and has been witnessing phenomenal growth in recent years. India is the third largest pharmaceutical market in terms of volume and thirteenth largest in terms of value, and is expected to grow further rapidly in coming years. The industry covers conventional as well as biological medicinal products including vaccines, pharmaceuticals, and medical devices.

India is emerging as a world leader in generic pharmaceuticals production, supplying 20% of the global market for generic medicines. Indian exports are

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destined to more than 200 countries around the globe including the highly regulated markets of the United States (U.S.), Western Europe, Japan and Australia. India is also a major vaccine producer with 21 major vaccine manufacturing facilities. The vaccines are used for the national and international market (150 countries) which makes India a major vaccine supplier across the globe.

The progress made in developing the pharmaceutical industry in India has increased the importance of its role both in domestic and export markets. However, one may speculate that the industry has developed somewhat more rapidly than the regulatory system. Thus, India is committed to building a strong, world class regulatory system.

India has a functional regulatory system for vaccines according to the criteria of the WHO Global Benchmarking Tool. This is a prerequisite for India-based vaccine manufacturers to apply for WHO prequalification of their products. The functionality of the regulatory authority was confirmed in February 2017 in a comprehensive WHO review of the NRA and affiliated institutions. India is supplying several prequalified vaccines to UN agencies, and this is expected to lead to more affordable vaccines being available on the global market. (2)

Indian manufacturers are the key contributors to the WHO prequalification of medicines programme, with 64% of the finished pharmaceutical products and 59% of the active pharmaceutical ingredients listed on WHO’s prequalification lists being produced in India. Recently, India has played a pivotal role in scaling up access to affordable hepatitis C medicines, and the first WHO-prequalified generic hepatitis C medicine is produced by an Indian manufacturer.

The government has invested large funds for strengthening the drug regulatory authority and drug testing laboratories in the 12th Five Year Plan of the Government of India (2012–17), enabling a range of initiatives and achievements in the regulatory sector. The government has recently invested US$ 275 million for strengthening the drug regulatory system in the country. There is also an upcoming National Drug Regulatory Academy for training of the regulators at central and state levels. (3) India is actively engaged in the new South East Asia Regulatory Network (SEARN) in a move to increase access to high-quality medical products in WHO Member countries in the South-East Asia Region.

The following sections provide an overview of the regulatory landscape of India, and of recent initiatives for regulatory systems strengthening in line with international standards.

Regulatory system

Legal basis

The Indian drug regulatory system originated in 1940, when the Drugs & Cosmetics Act was passed to address the sudden and rapid expansion of pharmaceutical production in the country. The Drugs Rules were framed in 1945 to give effect to the provisions of the Act. (4) Both the Act and Rules were subsequently amended many times, and various legislative texts were passed to regulate the import, manufacture, distribution and sale of drugs in India, including:

- The Pharmacy Act 1948;
- The Drugs and Magic Remedies (Objectionable Advertisements) Act 1954;
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Figure 1: Regulatory environment for health products in India

<table>
<thead>
<tr>
<th>Ministry of Health and Family Welfare</th>
<th>Ministry of Chemicals and Fertilizers</th>
<th>Ministry of Commerce</th>
<th>Ministry of Science and Technology</th>
<th>Ministry of Environment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Directorate General of Health Services (DGHS)</td>
<td>Department of Pharmaceuticals</td>
<td>Patent Office</td>
<td>Central Drugs Standard Control Organization (CDSCO) headed by Drug Controller General of India, DCGI (I)</td>
<td>Environmental clearance for manufacturing</td>
</tr>
<tr>
<td>+ Statutory Committees + Advisory Committees</td>
<td>+ State Licensing Authorities</td>
<td>National Pharmaceutical Pricing Authority (NPPA): Drugs (Prices Control) Order (DPCO) 2013</td>
<td>Controller General of Patents</td>
<td>Council of Scientific and Industrial Research (CSIR) Laboratories</td>
</tr>
</tbody>
</table>

- **Statutory Committees:** Drugs Consultative Committee (DCC) provide advice on technical matters and on making rules, and Drugs Technical Advisory Board (DTAB): securing uniform implementation of DCA and rules throughout India.

- **Advisory Committees:** Subject Expert Committees (SEC) drawn from relevant panels of experts advise on approvals of clinical trials, drugs and medical devices. New Drug Advisory Committee (NDAC) headed by Secretary, Department of Health Research, and Investigational New Drugs Committee (INDC) headed by Director General of ICPR, provide recommendations on approval of clinical trials. The Indian Council of Medical Research (ICMR) provides assistance in evaluation of Phase I clinical trials. Three-tier system for examination of clinical trials: NDAC/INDC / Technical Committee (TC) under chairmanship of DGHS / Apex Committee under the chairmanship of Secretary Health.

- For biologicals: Department of Biotechnology (DBT) supports DCG (I) in identifying, formulating, implementing and monitoring of various activities related to biotechnology e.g. through Division of Biologicals and the Cellular Biology-Based Therapeutic Drug Evaluation Committee (CBBTDEC).

- For medical devices (except investigational ones): Medical Devices Advisory Committee (MDAC) advises DCG (I) on review and approval of products and clinical trials.

- The Narcotic Drugs and Psychotropic Substances Act 1985;
- The Medicinal and Toilet Preparations (Excise Duties) Act 1956;
- The Drugs (Prices Control) Order (DPCO) 1995 (under the Essential Commodities Act), amended in 2013 to cover specified dosages and strengths under the National List of Essential Medicines (NLEM) 2011 and modified to include medicines in NLEM-2015;
- The National Pharmaceutical Pricing Policy, 2012 (NPPP-2012);
- The Patent Act Amendment 2015 (includes amendments in the Patent Act 2002); and
- The National Health Policy 2017. Today, most of the Indian health products are governed by the Drugs & Cosmetics Act, which covers a wide variety of drugs, therapeutic substances, diagnostics and medical devices. The regulatory mechanisms and are in line with relevant technical guidelines from international organizations such as WHO, the International Council on Harmonization of Technical Requirements...
for Registration of Pharmaceuticals for Human Use (ICH), the Pharmaceutical Inspection Co-operation Scheme (PIC/S) and others.

Regulatory environment
The regulatory environment in India is composed of several important stakeholders in the fields of biotechnology, biomedical sciences, agriculture, health care, animal sciences and environment industry (Figure 1).

International collaboration
India has actively contributed and provided support for the new South East Asia Regulatory Network (SEARN). The Indian national regulatory authority is also a member of the Developing Country Vaccine Regulators’ Network (DCVRN); an observer in ICH, and a Vice-Chair of WHO’s Member State Mechanism on substandard and falsified medical products¹. Mutual agreements and memoranda of understanding have been concluded with the NRAs of the United States, the United Kingdom, Japan, Russia, Sweden and other countries.

Regulatory authority
India is a federal union of 29 states and 7 union territories. Thus, the Indian drug regulatory system is divided into central (federal) and state (provincial) authorities.

Central Licensing Authority
The national regulatory authority of India is the Central Drugs Standard Control Organization (CDSCO) under the Directorate General of Health Services of the Ministry of Health & Family Welfare. CDSCO is headed by the Drugs Controller General of India, DCG (I). CDSCO has 379 staff members. There has been a steep rise in recruitment, and staffing increased from 111 positions in April 2008 to 474 sanctioned positions currently.

The mission of CDSCO is to safeguard and enhance public health by assuring the safety, efficacy and quality of drugs, cosmetics and medical devices. CDSCO discharges the functions assigned to the central government under the Drugs & Cosmetics Act.(4). The major functions of CDSCO are:

• Frame policy and procedures for uniform implementation of the provisions of Drugs & Cosmetics Act, 1940 and Rules, 1945 thereunder.
• Assist in setting and implementation of standards for Drugs, Cosmetics and Medical Devices through it.
• Coordinate and liaise with international organizations/bodies such as WHO, the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA), the Pharmaceuticals and Medical Devices Agency (PMDA) of Japan, the European Directorate for the Quality of Medicines & HealthCare (EDQM), the South Asian Association for Regional Cooperation (SAARC), the WHO Regional Office for South East Asia (SEARO), BRICS nations – Brazil, Russia, India, China and South Africa – and other counterparts.
• Exercise regulatory control over the import of medicines, approval of new medicines and clinical trials, conduct meetings with the Drugs Consultative Committee (DCC) and Drugs Technical Advisory Board (DTAB), and act as Central Licence Approving Authority (CLAA) for approval of certain licences.
• Carry out joint inspections through the Zonal Offices and coordinate actions

¹ http://apps.who.int/gb/SSFFC/
with the state Drugs Controllers under their jurisdiction.

- Exercise quality control of imported medicines through the port offices.
- Maintain drugs testing laboratories for testing of samples.

CDSCO has a number of affiliated institutions under its control (Figure 2). These include the Central Drugs Laboratory (CDL) in Kasauli, Himachal Pradesh state and the Pharmacovigilance Programme of India at the Indian Pharmacopoeia Commission (IPC) in Ghaziabad, Uttar Pradesh state. CDSCO has six Zonal Offices, five Sub-Zonal Offices (including one created recently at Indore in Madhya Pradesh state) with another being established at Guwahati in Assam state, 13 port offices and eight laboratories under its control. The Zonal Offices work in close collaboration with the state Drug Control Administrations and assist them in securing uniform enforcement of the Drugs & Cosmetics Act and related legislation on an all-India basis. Quality control of imported medicines is performed by the port offices, where samples are taken and forwarded to the drug laboratories for testing.

The main statutory function of the laboratories\(^2\) is to perform analytical quality control as part of quality monitoring performed by the regulatory authorities for imported medicines and those manufactured within the country. Other functions of the laboratories are to undertake analytical research on standardisation and methodology of pharmaceutical products and cosmetics; undertake analysis of cosmetics survey samples received from CDSCO, and quick quality control analysis of life-saving medicines on an all-India basis received from CDSCO Zonal Offices under the National Survey of Quality of Essential Drug Programme.

The Indian Pharmacopoeia Commission (IPC), which hosts one of the three WHO-prequalified medicines quality control laboratories in India, is also involved in testing of imported and new pharmaceuticals. The laboratory has special functions as it is also engaged in preparation and maintenance of national reference standards, training of drug analysts and regulators in quality control analysis, and

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development of analytical specifications for preparation of monographs of the Indian Pharmacopoeia.

State Licensing Authorities
At the state level, authorities consist of Food and Drug Administrations (FDA) – one for each state – and certain licensing authorities for the Union Territories (i.e., areas administered by the Union Government directly). The regulation, manufacture, sale and distribution of drugs are primarily the concern of state authorities. The state FDAs also control the quality of food articles, manufactured and sold within the state as well as manufactured outside the state but sold in the state. The functions of the State Licensing Authorities include:

- Licensing of manufacturing site for drugs including API and finished formulation;
- Licensing of establishment for sale or distribution of drugs;
- Approval of drug testing laboratories;
- Monitoring of quality of drugs and cosmetics marketed in India;
- Investigation and prosecution in respect of contravention of legal provision; and
- Recall of substandard drugs.

Regulatory system strengthening

Resources
There has been a steep rise in budget allocation for regulatory strengthening at central and state levels in India. For the financial year 2012–2013 the budget allocation was Indian Rupee (INR) 0.58 billion (approx. US$ 8.7 million), which was raised to INR 4.3 billion (approx. US$ 64.8 million) in the financial year 2015–16. The 12th Five Year Plan envisages a total of 17.5 billion INR (approx. US$ 273 million) for strengthening the drug regulatory structures both at central level3 and state level4.

The increased investments have led to strengthened regulatory manpower, infrastructure, systems and processes. There is provision for scaled-up manpower, new laboratories, an E-Governance portal and a National Drug Regulatory Academy for training of regulators at central and state levels, as described below.

Quality management system (QMS)
There is an established QMS at CDSCO and its affiliated institutions. A quality policy has been established and there are documented quality manuals, standard operating procedures and instructions. Trainings and learning are planned and organized under an institutional development plan. The outcomes of engagements and regulatory processes are published on the website to ensure transparency. Target timelines are established for regulatory processes.

Resource allocation for the QMS is from the Quality Assurance (QA) Division and Biological Division. There is well-established coordination with other institutions, teams and departments/divisions. The Quality team is composed of the respective Divisional Head and staff along with QA Department. Their major functions are to undertake internal and external audits and to obtain ISO certification. Certification under ISO 9001-2008 has been achieved by CDSCO Headquarters, the Zonal Offices of Ahmedabad, Hyderabad, Ghaziabad

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3 CDSCO: INR 9 billion for setting up new laboratories to test drugs, medical devices, cosmetics and diagnostics kits, upgrading existing laboratories, establishing an e-Governance system, construction of new CDSCO offices, creating additional posts, establishing a Training Academy, and conducting IEC activities.

4 States: INR 8.5 billion for laboratory manpower and infrastructure, inspectorates, mobile testing laboratories, IT enabling E-governance, and training.
and Kolkata, and the Sub-Zonal Office Chandigarh.

E-governance
An E-governance system has been launched in India through a portal named SUGAM5 – literally meaning “ease” or “facilitation” – for on-line processing of applications. The system links the CDSCO headquarters with other offices, laboratories and state authorities. The following CDSCO activities are currently performed through the SUGAM portal:

- Import registration and licensing of drugs and medical devices
- Registration of cosmetics
- Registration of ethics committees
- Permission to conduct clinical trial
- Permission to conduct bioavailability and bioequivalence study for export purpose
- Personal permit for import of drug by individual patient
- Test licence for import of small quantities of drugs for test and analysis purpose.

On-line processing of protocols at CDL, Kasauli and of bills of entries at all CDSCO port offices have been integrated with the customs online system called ICEGATE. The SUGAM portal will also be linked to the state regulatory authorities for online issuance of licences.

The SUGAM portal has been awarded the Computer Society of India (CSI)’s Nihilent e-Governance Award of Excellence 2016.

WHO Certification Scheme
The WHO-recommended Certificate of Pharmaceutical Product (CPP) format6 serves to establish the status of a pharmaceutical product and of the applicant for the certificate in the exporting country. It is issued for a single product only, since manufacturing arrangements and approved information for different dosage forms and different strengths can vary. A CPP is a legal requirement in many countries for imported products submitted for marketing authorization.

After each joint CDSCO and state licensing authority inspection of the manufacturing plant, the drug regulator issues a CPP. Currently 1314 manufacturing units and 10 Ayurvedic manufacturers in India have been granted CPPs for their products.

Training
CDSCO and the Ministry of Health & Family Welfare are continuously engaged in imparting training to the drugs regulatory officials and laboratory personnel at central and state levels. Thirty-six training programmes/workshops on the various subjects related to the drug control were held in 2014–15. From October 2015 to May 2017, 10 training programmes including induction as well as advanced-level programmes were organized, about 700 officials were trained. The approved training schemes also entail setting up a National Academy for Drug Regulators.(1) Based on the WHO NRA strengthening Institutional Development Plan, several capacity-building activities focusing primarily on the regulatory inspection function had been organized by WHO during the past years, including several basic as well as advanced workshops for conducting Good Manufacturing Practices (GMP) inspections using a quality risk approach.
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Regulatory functions

Control of clinical trials

Good Clinical Practices (GCP) is an ethical and scientific quality standard for designing, conducting and recording clinical trials that involve the participation of human subjects. Compliance with this standard provides assurance to public that the rights, safety and well-being of trial subjects are protected, consistent with the principles enshrined in the Declaration of Helsinki, and ensures that clinical trial data are credible.

The Indian GCP guidelines (9) were formulated by an Expert Committee set up by CDSCO in consultation with clinical experts, and endorsed by Drug Technical Advisory Board (DTAB). The guidelines are intended to ensure uniform quality of clinical research throughout the country and generate data for registration for new drugs before use in the Indian population.

The role of CDSCO is to review, evaluate and approve or reject clinical trial applications, inspect clinical trial sites, register and monitor ethics committees, and decide on compensation in case of serious adverse events related to clinical trials.

Clinical trial approvals are granted by the Drugs Controller General of India (DCGI), in line with Schedule Y of the 1940 Drugs & Cosmetics Act. An applicant who wishes to conduct a clinical trial has to submit an application to the DCGI along with full product details, animal pharmacology and toxicity data, animal toxicology and clinical data (if available), the trial protocol, and information about the regulatory status of the product in other countries. Applicants also have to report any suspected or unexpected serious adverse reaction (SUSAR) of the product in other countries.

It is the responsibility of the institutional ethics committees (IECs) to review and monitor clinical trials for compliance with ethical guidelines. The role of the IECs is to review the safety reports, the informed consent document, and any violations of the ethical guidelines.

The Indian Council of Medical Research (ICMR)’s 2006 Ethical guidelines for biomedical research on human

Table 1: Timelines for registration & marketing authorization functions

<table>
<thead>
<tr>
<th>Type of Application</th>
<th>Target timeline (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Trial</td>
<td>180</td>
</tr>
<tr>
<td>Marketing Authorization</td>
<td>180</td>
</tr>
<tr>
<td>Registration Certificate for Import</td>
<td>270</td>
</tr>
<tr>
<td>Form 28-D (Manufacturing Licence)</td>
<td>60</td>
</tr>
<tr>
<td>Form 29 Non-Objection Certificate (NOC)</td>
<td>60</td>
</tr>
<tr>
<td>Licence to manufacture Pre-approval batches</td>
<td>60</td>
</tr>
<tr>
<td>Validity of the permission to manufacture pre-approval batches has been increased from 1 year to 3 years</td>
<td>60</td>
</tr>
<tr>
<td>Import Licence (Form 10)</td>
<td>45</td>
</tr>
<tr>
<td>Test Licence (Form 11)</td>
<td>45</td>
</tr>
<tr>
<td>Validity for import of reference /test / investigational vaccines has been increased from 1 year to 3 years</td>
<td>45</td>
</tr>
<tr>
<td>Export NOC for Biological Samples</td>
<td>45</td>
</tr>
<tr>
<td>Post Approval Change (Major)</td>
<td>180</td>
</tr>
<tr>
<td>Post Approval Change (Minor)</td>
<td>90</td>
</tr>
</tbody>
</table>
participants (10) have been accepted as the standard operating manual by IECs in India. A proposed update to these guidelines was finalized for public comment at regional and national consultation meetings jointly organized by ICMR and the WHO Country Office for India in 2016. ICMR also maintains the Clinical Trials Registry of India (CTRI), a primary registry under the WHO International Standards for Clinical Trial Registries (ICTRP).

Various achievements have promoted the scientific and ethical conduct of clinical trials in India. Additional requirements have been introduced for the informed consent process, and audio-visual recording has become mandatory to protect vulnerable subjects in line with international best practice. A three-tier system of scrutiny of proposals of clinical trials by the New drugs Subject Expert Committee (SEC)/ Investigational New Drugs Committee (INDC), under the Chairmanship of Directorate General Health Services and Apex Committee under the chairmanship of Secretary Health, has been established (see also Figure 1). Since 2011, registration of ethics committees with the licensing authority is mandatory. New rules are in place for inspections of clinical trials. A rationalized definition of injury has been introduced, and – for the first time in the world by any regulator – exact procedures have been specified for payment of compensation, based on a formula, to subjects to cases of injury or death occurring on account of clinical trials.

A handbook on clinical trial applications was published in January 2017, (11) and training of Subject Expert Committee members and CDSCO reviewers has been stepped up.

Timelines for review of clinical trial applications have been reduced with the expansion of Subject Expert Committee panels and the introduction of an online submission process. Timelines for serious adverse event reporting by investigators, ethics committees and Sponsors have also been rationalized. For clinical trials of recombinant DNA-derived products a parallel submission process to Review Committee on Genetic Manipulation (RCGM) and CDSCO has been introduced.

Registration functions and timelines
Registration and marketing authorization in India includes various processes. An important addition was the amendment of the Drugs & Cosmetics Rules to require bioavailability/bioequivalence studies studies for oral formulations of drugs belonging to the biopharmaceuticals classification System (BCS) Class II and IV before licensing.

Target timelines have been set for the different functions related to marketing authorization (Table 1). In recent years there has been a reduction of the timelines for regulatory approvals. A timeline of 30 working days has been specified for the CDL, Kasauli to review and provide opinion on Module 3 of the Common Technical Dossier (CTD) submitted as part of marketing authorization applications. Approval processes have been simplified as the Subject Expert Committees have to communicate their recommendations on approval of clinical trials and marketing authorizations within five working days.

GMP and regulatory inspections
Inculcating good manufacturing practices (GMP) for pharmaceutical or biological products is an essential regulatory
function. Since a consumer cannot detect whether a medicine s/he is taking is safe and effective, it is important that products are manufactured under conditions and practices required by GMP regulations.

Most of the GMP requirements in India are specified under the “Schedule M” of the Drugs & Cosmetics Act 1940. Schedule M specifies the GMP requirements for products such as pharmaceuticals, medical devices and vaccines, and gives detailed specifications on infrastructure, premises, environmental safety, health measures, production, operation controls, quality control, quality assurance, stability, validation and other related areas. The protocols under Schedule M have been amended many times to harmonize it with internationally accepted standards such as WHO-GMP and U.S. FDA guidelines.

GMP inspections of manufacturing units are carried out by qualified inspectors from CDSCO along with inspectors from state Drug Control and product experts from CDL. Inspections are conducted for 2–5 days depending on the size of the unit, the number of products handled and the complexity of products and procedures. Various types of inspection are conducted, including: Pre-approval inspection of the site for grant or renewal of licence; routine annual inspection; for-cause inspection/complaint investigation; inspection subsequent to post approval changes; risk-based inspection; and inspection for issuance of a Certificate of Pharmaceutical Product (CPP) for the purpose of export. Inspections are planned on a risk basis.

The regulatory actions for non-compliances are defined in Rule 85 of the Drugs & Cosmetics Rules and include regulatory letters requiring measures to address the deficiencies, suspension or cancellation of licences and legal prosecution of the manufacturer.

**Licensing of premises**

Under the Drug and Cosmetics Act (4) the regulation of manufacture, sale and distribution of medicines is primarily the responsibility of the state authorities. DCG (I) is responsible for approval of licences of specified categories of products, *i.e.* biological products including vaccines, blood and blood products, I.V. fluids and notified medical devices. Rule 68-A provides for Grant or Renewal of Licences by the Central Licence Approving Authority.

Both the state and central authorities have adequate competent staff to perform licensing of premises and control activities. 179 drugs inspectors are working in CDSCO, recruitment of additional inspectors is under way and a new post category of Assistant Drugs Inspectors (ADIs) has been created. Approximately 1333 inspectors work in the state authorities.

**Control of imported products**

The CDSCO regulates the quality of medicines imported into the country, including registration of overseas manufacturing sites and drug products including both bulk drugs and finished formulations. The quality of imported medicines is further monitored at the port offices. For imported cosmetics, registration was initiated from 1st April, 2013 to ensure that products are of standard quality and have been manufactured under GMP by genuine, licensed manufacturers. (7) In 2014, the Drugs & Cosmetics Rules were amended to prohibit the testing of cosmetics on animals, and in the same year the prohibition was extended to imported cosmetics.
CDSCO and state authorities fulfill this function as provided in laws, rules and guidance documents, and as agreed in Drugs Consultative Committee meetings. There are designated inspectorates at state and central level, and port officers controlling import and export of products. A state inspector in each district performs sampling; central inspectors also do risk-based sampling. If products are found to be not of standard quality, investigations are carried out and appropriate actions taken such as suspension or cancellation of licences, launching of prosecution, and recalls. Guidelines on Recall and Rapid Alert System for Drugs (12) and on Good Distribution Practices for Biological Products (13) have been circulated all over the country.

During 2014-2016 the Ministry of Health & Family Welfare undertook the largest-ever survey in the world for determining the quality of pharmaceuticals. As part of this survey, 47,954 drug samples relating to 23 dosage forms were drawn from 654 districts of 36 states and union territories from the supply chains including retail outlets and government sources and from eight airports and sea ports. In many ways, this Survey of Extent of Problems of Spurious and Not of Standard Quality Drugs in the Country was the first of its kind, and the largest ever scientifically designed and professionally executed drugs survey conceptualised to understand the quality of drugs being sold in the domestic market of India. The survey found that 3.16% of the samples tested were Not of Standard Quality (NSQ), and 0.0245% were spurious. (14)

Control of promotional materials

Unlike package inserts of drugs, promotional materials are not pre-approved. However, false claims or advertisements are detected by random checks and complaints and are punishable under general law and under the Drugs and Magic Remedies (Objectionable Advertisement) Act, 1955.

Pharmacovigilance

WHO has been playing a pivotal role in supporting health product regulation in India at both central and state levels, particularly in strengthening the vigilance of medical products. The Indian Pharmacopoeia Commission (IPC) has recently been designated as the first WHO Collaborating Centre for capacity-building for pharmacovigilance in public health programmes and regulatory services in the WHO South-East Asia Region. (15)

Medicines

The Pharmacovigilance Programme of India (PvPI) was initiated by CDSCO in 2010. Its functions are to create a nationwide system for ensuring patient safety through better adverse drug reaction reporting; to identify and analyze new signals on adverse drug reactions (ADRs) from reported cases; to analyze the benefit/risk ratio of marketed medications; to support regulatory agencies in the decision-making process on use of medications; to communicate the safety information on use of medicines to various stakeholders to minimize risks; to collaborate with other national centres for the exchange of information and data management; and to provide upon request training and consultancy support to other pharmacovigilance centres globally.

PvPI has a Steering Committee, several Working Groups and three panels for Signal Review, Quality Review and Core Training. The Signal Review Panel (SRP) periodically analyzes individual case safety reports (ICSRs), identifies safety signals and
provides recommendations on any needed regulatory actions to CDSCO.

Reports on suspected ADRs can be submitted by health care professionals and consumers. Drugs & Cosmetics Act & Rules was amended by Gazette notification GSR no. 287 (E) dated 8th March 2016, mandating all manufacturers and importers for setting up a pharmacovigilance system managed by qualified and trained personnel within their company.

Most reports are received from local ADR Monitoring Centres (AMCs). The Programme started with 22 AMCs and as on January 2017 has 210 centres across the country. Of these, 17 receive information from the Revised National Tuberculosis Control Programme (RNTCP), 20 from the HIV control programme on anti-retroviral therapy, and 6 are designated as Bedaquiline Centres. The recent PvPI focus on cohort event monitoring of bedaquiline is a classic example of a response to newer drugs of national importance.

The ICSRs collected under PvPI are also submitted into the WHO global database of adverse drug reactions called VigiBase. VigiBase is hosted by the WHO Collaborating Centre for International Drug Monitoring – Uppsala Monitoring Centre (UMC).

Vaccines
A surveillance programme to monitor adverse events following immunization (AEFI) was initiated in India in 1988. In 2005, the Government of India, with technical assistance from WHO, drafted the National AEFI Surveillance and Response Operational Guidelines, which were subsequently revised in 2010 and 2015.(16)

Vaccine pharmacovigilance in India is handled in close cooperation by three partner agencies: CDSCO, the AEFI Division under the Ministry of Health & Family Welfare, and the IPC’s PvPI. Many public sector AEFI surveillance workshops have been conducted throughout the country. A QMS has been established, guidance documents and standard operating procedures published, training provided, and a pilot online reporting project introduced. As a result, AEFI reports have increased from 398 in 2012 to 1393 in 2016. However, AEFI surveillance in the private sector is still very limited and needs attention, as it also contributes a critical part in the immunization process.

The Pharmacovigilance Division (Human vaccine) within CDSCO’s Biological Division monitors all post-licensure activities for vaccines including reporting of AEFI, periodic safety update reports (PSUR) and any other data on adverse reactions. CDSCO decisions are taken based on analyses of these data by an expert committee, recommendations from the National AEFI Committee, and investigations including testing of samples as and when required. On the recommendations of the PSUR expert committee CDSCO will generally request marketing authorization holders to set up a pharmacovigilance system within their company, to conduct active surveillance for collection of AEFI data, and/or to update package inserts to include any additional warnings or information as appropriate.

Blood products
The Haemovigilance Programme of India (HvPI)10 was launched in 2012 as a fundamental component of the Pharmacovigilance Programme of India (PvPI). Its objective is to monitor

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10 http://www.nib.gov.in/haemovigilance.html
adverse events related to blood products all along the transfusion chain. Currently, 154 centers have been enrolled in this programme. Information obtained is filled in the Transfusion Reaction Reporting Form (TRRF) and transmitted to the National Coordinating Centre at the National Institute of Biologicals (NIB) using the Hemovigil® software. The NIB’s recommendations based on the collected data are forwarded to the National Coordinating Centre at IPC for further transmission to CDSCO.

The haemovigilance programme is functional through a core group and an advisory committee, which coordinate the haemovigilance activities between medical colleges and the National Coordinating Centre and provide expert opinions for analysis of the information generated. The advisory committee also provides helpful insights in linking HvPI with the International Hemovigilance Network (IHN).

**Regulation of medical devices**

The medical devices sector is one of the 25 focus sectors identified under the “Make in India” campaign, which was launched in 2014 by the Indian government to make India a global manufacturing hub and bring foreign technology and capital into the country. Similarly, the National Medical Device Policy 2015 aims at reducing dependence on imports of medical devices and equipment. To facilitate investments the Cabinet has allowed foreign direct investment of up to 100% under the automatic route for manufacturing of medical devices subject to specified conditions.

Various initiatives are under way to promote the medical device industry. A scheme for financing common facility centres at medical device parks is under consideration under the umbrella of the “Development of Pharmaceuticals Industry” scheme to create an ecosystem for high-end medical device manufacturing and import substitution with an eye on the for-export market. Corrections have been introduced in the inverted duty structure: Import duty on certain product categories has been raised and exemption from special additional duty (SAD) withdrawn, while basic customs duty has been reduced and SAD waived on raw materials. Furthermore a proposal is under consideration for giving preference to domestic manufacturers in purchase of medical devices by government agencies. A Uniform Code for Medical Device Marketing Practices has been drafted for comment by stakeholders. Lastly, a proposal is under consideration to set up a Medical Device Promotion Council at Vishakhapatnam in co-operation with Andhra Pradesh MedTech Zone Ltd. (AMTZ). The Council will act as a facilitating and promotional body for domestic medical devices.

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These moves are strongly supported by the recently notified regulatory framework for medical devices, which will come into force on 1 January 2018. It is encouraging that this framework is based on international standards. The new Rules have been framed in conformity with the Global Harmonization Task Force (GHTF) framework in line with best international practices. The amended Drugs & Cosmetics Act will also regulate the import, manufacture, distribution and sale of medical devices.

Monitoring of adverse events related to medical devices, including in vitro diagnostic products, is an important component of regulatory control, as their performance depends to a considerable extent on their appropriate use. A system is in place for this purpose through the Materiovigilance Programme of India (MvPI)\(^{11}\), launched in 2015 under the umbrella of PvPI. There are 10 Medical Device Monitoring Centres (MDMCs). Adverse events are reported by a wide range of stakeholders supplying or handling CDSCO-notified medical devices. Reports are recorded on the Medical Device Adverse Event (MDAE) reporting form, which is forwarded by the MDMCs to the National Collaboration Centre. IPC receives technical support from the National Health System Resource Centre (NHSRC) and collaborates with the Sree Chitra Tirunal Institute for Medical Sciences and Technology (SCTIMST) in providing advice to CDSCO on regulatory actions for medical devices.

The Indian medical device sector continues its upward march of growth and is strongly supported by India’s robust notified regulatory framework, including the Materiovigilance Programme of India (MvPI) described above which has been formulated by the Government of India as a system of reporting of adverse events related to medical devices.\(^{(17)}\)

**Conclusions**

India’s pharmaceutical market has expanded rapidly, and India is increasingly important for the production of vaccines, generic medicines and other pharmaceutical products. Improving access to medical products is central to the achievement of universal health coverage. Strategies to improve access also need to be linked to the safety and quality assurance of all medical products. The need to expand access to medicines and health products is highlighted in the United Nations’ Sustainable Development Goals (SDGs) specifically in two targets and more broadly in at least seven other targets under Goal 3 of the SDGs.

Access to health products will be a key indicator for countries’ progress to universal health coverage. This gives an opportunity to build on progress made so far and help to bring about access to quality essential medicines and health products for all.

Developing and supporting regional networks for regulatory cooperation and building capacity of national regulatory authorities will be a major element of this priority. India has actively contributed and provided support for the new South East Asia Regulatory Network (SEARN) in a move to guarantee access to high-quality medical products in the WHO South-East Asia Region Member countries.

There have been many examples of the Indian government’s commitment towards strengthening the regulatory systems of the country. India also has to its advantage access to a pool of highly skilled personnel.\(^{11}\) http://ipc.nic.in/index1.asp?EncHid=&dlang=1&dlinkid=82&lid=548
scientists and R&D facilities that can help in developing novel products with lower production costs.

Health care has become one of the key priorities of the Indian Government, and new policies and programmes have been launched to boost local access to affordable, quality health care. The Union Budget 2017–18 shows an increase of 23% in health expenditure that is likely to give further impetus to the pharmaceutical sector. The government, as part of the Budget, has proposed amendments to the Drugs & Cosmetics Rules to ensure availability of generic drugs at reasonable prices and promote their use. The government has also introduced a range of fiscal incentives to promote domestic manufacturing, including the reduction of inverted duty structure and basic customs duty.

A robust medical products regulatory system in India can help the country realize the Prime Minister’s vision of “Make in India” and channel political commitment and resources in this important direction. It is important to point out that regulatory systems strengthening is an integral part of overall health systems strengthening which is vital for achieving medical products related Sustainable Development Goal 3: Good Health and Well-being, and WHO aspirations of achieving Universal Health Coverage (UHC). In conclusion, we believe that building up a modern, robust and efficient regulatory system in India is a good investment in public health not only for Indians but also globally.

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