CHAPTER 9
INDIA

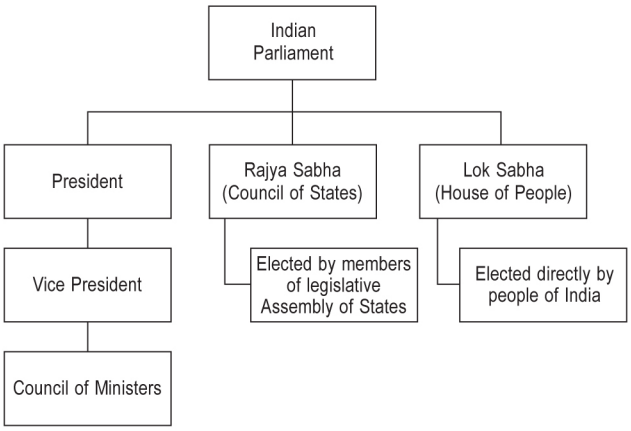
BY MILIND ANTANI AND KHUSHBOO BAXI

Legal System

The Constitution of India is the fundamental source of law in India. It gives due recognition to statutes, case law and customary law, all of which contribute to India's legal system. The legal system itself is primarily a common-law jurisdiction.

According to the Constitution, India is a "sovereign, socialist, secular, democratic republic." It has a federal form of government, with the central government exercising significantly greater power than that of its states. The constitution provides for three branches of government: legislative, executive and judiciary.

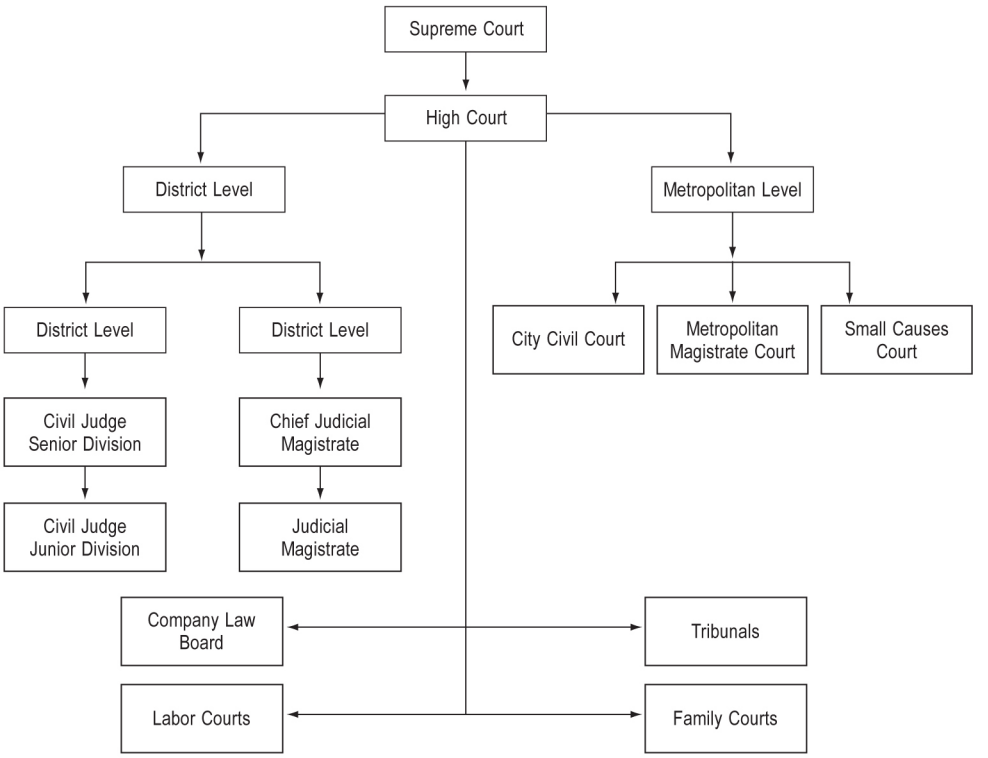
India's Parliament (Sansad) is the supreme legislative body. It includes two houses: the Lok Sabha or "House of the People" has up to 552 members, nearly all of whom are directly elected by the citizens of India; the Rajya Sabha or "Council of States" has 250 members elected by the legislative bodies of India's 28 states, with 12 members nominated by the president for special knowledge in literature, science, art or social services.



The president of India convenes Parliament, can summon Parliament to meet and must give his assent to all parliamentary bills before they become law. The Council of Ministers, led by the prime minister, holds a larger measure of real national executive power. The prime minister is designated by lawmakers of the political party or coalition with parliamentary majority and then officially appointed by the president. The president then appoints subordinate ministers on the advice of the prime minister.

The judiciary is the interpreter and guardian of the Constitution. A single unified court system is responsible for both state and federal laws. This is a unique feature of India's government.

The Supreme Court of India[1] is at the apex of the entire judicial system, followed by High Courts in each state or group of states. Below the High Courts lie numerous District Courts and tribunals. A vast number of people in India reside in villages and fall under the jurisdiction of Panchayat Courts, which decide civil and criminal disputes of a petty and local nature.



The Constitution has clearly demarcated the power given to each branch of government and has enabled each to provide a system of checks and balances on the other. The basic concept is to promote harmony among the working practices and restrict each of the branches to acting within their own spheres of authority. For instance, the legislative branch must function within the limitations of the written Constitution: its lawmaking powers are subject to the condition of being in consonance with the provisions of the Constitution, the power of checking which is given to the judiciary.

Each state is divided into judicial districts presided over by a District and Sessions Judge, which is the principal civil court of original jurisdiction. The Sessions Judge is the highest judicial authority in a district. Below him, there are courts of civil jurisdiction, known in different states as Munsifs, Sub-Judges, Civil Judges and the like. Similarly, the criminal judiciary comprises the Chief Judicial Magistrates and Judicial Magistrates of the First and Second Class.

As far as the courts are concerned, matters relating to pharmaceutical law interpretations are tried by the High Courts in the state in which jurisdiction lies and the Supreme Court. At the tribunal level, matters relating to the protection and enforcement of intellectual

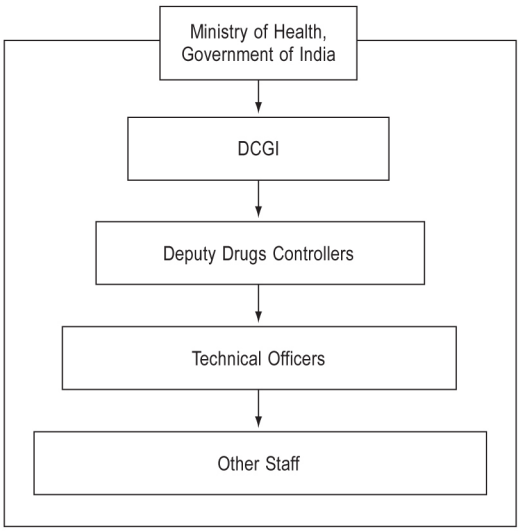
property rights (trademarks and patents) are heard by the Intellectual Property Appellate Board.

Key Legislation and Agencies

The Central Drugs Standard Control Organization and the Drugs Controller General of India; The DC Act and DC Rules

The Central Drugs Standard Control Organization (CDSCO),[2] headed by the Drugs Controller General of India (DCGI), is primarily responsible for coordinating the activities of the State Drugs Control Organization, formulating policies and ensuring uniform implementation of the Drugs and Cosmetics Act of 1940 (DC Act)[3] and the Drugs and Cosmetics Rules of 1945 (DC Rules)[4] throughout India. Within the CDSCO are authorities located in each state for the purpose of granting approvals for setting up manufacturing facilities, obtaining licenses to sell and stock drugs, and regulating inter- and intrastate commerce in drugs. The CDSCO functions under the Directorate General of Health Services.

The DC Rules prescribe the procedural aspects of the provisions of the DC Act. Under the DC Act and DC Rules, DCGI is the apex statutory, executive and quasi-judicial body at the central level. DCGI is also the only licensing authority for granting permission to conduct clinical trials in India.[5]



The Central Government has established four zonal offices of the CDSCO at Mumbai, Kolkata, Chennai and Ghaziabad. These zonal offices work in close collaboration with the

State Drugs Control Administration and assist in securing uniform enforcement of the DC Act and other related legislation on a pan-India basis. Matters of product approval and standards, clinical trials, introduction of new drugs and import licenses for new drugs are handled by DCGI. DCGI acts as the centralized License Approval Authority for certain categories of drugs. The DC Act and the DC Rules provide procedures for obtaining those approvals.

Approvals for setting up manufacturing facilities, obtaining licenses to sell and stock drugs and regulating inter- and intrastate commerce in drugs are some of the roles played by the respective state governments.

CDSCO has outlined provisions for product standards in concert with the DC Act and DC Rules. No drug can be imported, manufactured, stocked, sold or distributed unless it meets the quality and other standards set forth in the DC Act. For instance, for patented or proprietary medicines (i.e., medicines not listed in the Indian or other pharmacopoeia), the product should comply with the ingredients displayed in the prescribed manner on the label or container and other such standards prescribed by the DC Rules. General standards for all patent or proprietary medicines, tablets, capsules, liquid orals, injections and ointments are also in place under the DC Rules, which dictate that these should not be misbranded, adulterated or spurious.

A decision by DCGI to approve a new drug is dependent on its having a satisfactory balance of benefits and risks based on information available at that time. Once a product is marketed, it is understood that new information will be generated that may have an impact on the product's benefit-risk profile. This is known as postmarketing surveillance[6] of the product.

Schedule Y

The legislative requirements of pharmacovigilance in India are guided by specifications of Schedule Y[7] of the DC Act and the DC Rules thereto.

Schedule Y sets forth, for example, regulations pertaining to preclinical and clinical studies for the development of a new drug, as well as clinical trial requirements for the import, manufacture and receipt of marketing approval for a new drug in India. To this end, Schedule Y includes the approval procedures for clinical trial and other documentation to be submitted with the sponsor's application, with attention to the responsibilities of the sponsor, requirements of informed consent, responsibilities of Ethics Committees and details of the four phases of trials. Schedule Y also requires compliance with Good Clinical Practice Guidelines issued by CDSCO, the Directorate General of Health Services and the government of India.

Schedule Y underwent thorough review several years ago. Its latest amendment, dated January 20, 2005, aimed to underscore the continued commitment of DCGI to ensure pharmaceutical companies' adequate compliance with pharmacovigilance obligations. The amended Schedule Y also attempts to better define the responsibilities of pharmaceutical companies for their marketed products, as well as responsibilities for reporting adverse events from clinical trials. For a complete understanding of reporting responsibilities specific to clinical trials conducted in India, Schedule Y should be read along with Rules 122A, 122B, 122D, 122DA, 122DAA and 122E of the DC Rules.

As specified in Schedule Y, a pharmaceutical company holding one or more marketing licenses in India should ensure that it has in place an adequate pharmacovigilance system for its product(s). When two or more marketed products are identical in all aspects except their trade names, each pharmaceutical company holding a marketing license is obliged to independently meet their own pharmacovigilance obligations. This includes the establishment and maintenance of appropriate systems to collect, collate and evaluate information about suspected adverse reactions. A pharmaceutical company can achieve this either by setting up in-house systems for pharmacovigilance or by entering into contractual agreements with Contract Research Organizations (CROs) specializing in pharmacovigilance functions.

The National Pharmacovigilance Program

The National Pharmacovigilance Program (NPP) is a nationwide program in India sponsored and coordinated by CDSCO to establish and manage a database of adverse drug reactions (ADRs) for making informed regulatory decisions regarding marketing authorization of drugs in India. The NPP, which is sponsored by the World Health Organization (WHO) and funded by the World Bank, became operational in January 2005. Rather than a regulatory scheme *per se*, the NPP is primarily advisory and scientific.

NPP Objectives, Milestones and Functions

The official objectives[8] of the NPP are to

- contribute to the regulatory assessment of benefit, harm, effectiveness and risk of medicines, encouraging their safe, rational and more effective (including cost-effective) use;
- improve patient care and safety in relation to the use of medicines and all medical and paramedical interventions;
- improve public health and safety in relation to the use of medicines; and

- promote understanding, education and clinical training in pharmacovigilance and its effective communication to the public.

Three major milestones[9] frame these objectives:

- Short-term: To foster a culture of notification.
- Medium-term: To engage several healthcare professionals and nongovernmental organizations in the drug monitoring and dissemination processes.
- Long-term: To achieve such operational efficiencies that would make the NPP a benchmark for global drug monitoring endeavors.

Some of the major functions of this program include the monitoring of spontaneous ADRs, review of the Periodic Safety Update Reports (PSURs) submitted by the pharmaceutical companies and the assessment of safety information toward appropriate recommendations on product label amendments, product withdrawals and suspensions. NPP has its own form for spontaneous ADR reporting, and its protocol provides guidance to healthcare professionals on how to complete it when necessary.[10]

In recent years, the office of CDSCO has been making sincere attempts to expand implementation of the NPP[11] throughout India. While it readily acknowledges that "adverse drug reaction monitoring in India is still in its infancy," the government has emphasized its determination "to establish a vibrant, sustainable and credible adverse drug reaction monitoring programme [sic] in the country."[12]

Reporting

Single Case Reports

All reports from all sources involving serious unexpected adverse reactions must be reported to DCGI within 15 days of the applicant's initial receipt of the information regardless of whether they have been included in the PSUR.

Periodic Safety Update Reports

PSURs provide regulators in India with an update of the worldwide safety data of a marketed drug, biological product or device at defined time intervals. PSURs are considered to be an especially important pharmacovigilance tool: in India, they are required to include the safety data on a particular drug from all sources and geographical regions. This and other requirements for PSUR submission can be found in Schedule Y.

In a PSUR, an applicant is required to capture all relevant new information for DCGI review. That information should include recent safety data on the product from all appropriate sources; analysis of how that data relates to patient exposure; a summary of the product's market authorization status in different countries; notice of any significant variations related to safety; and an indication of whether changes should be made to product information to ensure the product's safe and appropriate use. In addition, any new studies planned or recently conducted to examine a safety issue should also be described in the PSUR. A PSUR should also give attention to whether further investigations need to be carried out and what changes might need to be made to the product's package insert. The format of the PSURs provided in Schedule Y is in accordance with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines.

PSUR Reporting Cycle

The PSURs are required to be submitted to DCGI every six months for the first two years after approval of the drug is granted. Subsequently, for the following two years, PSURs are required to be submitted annually.[13]

All single cases involving serious unexpected adverse reactions should be reported to DCGI within 15 days of the applicant's initial receipt of the information and must also be included in the PSUR.

Format of PSURs

Schedule Y prescribes the format of a PSUR as follows:

(a) A title page stating "Periodic Safety Update Report for the [named] product," applicant's name, period covered by the report, date of approval of new drug, date of marketing of new drug and date of reporting;

(b) Introduction;

(c) Current worldwide market authorization status;

(d) Update of actions taken for safety reasons;

(e) Changes to reference safety information;

(f) Estimated patient exposure;

(g) Presentation of individual case histories;

(h) Studies;

(i) Other information;

(j) Overall safety evaluation;

(k) Conclusion;

(l) Appendix providing additional material relating to indications, dosing, pharmacology and other related information.

Period of Reporting in PSURs

Schedule Y further states that if the marketing of a new drug is delayed after obtaining the approval to market it, such data may be submitted on a deferred basis beginning from the time the new drug is marketed in India. This is in sharp contrast to European Union regulations, where a pharmaceutical company is required to meet pharmacovigilance obligations of all the products for which it holds a marketing authorization, irrespective of their marketing status.

In Schedule Y, there is no distinction made between foreign and domestic reports and the time frame for reporting adverse events for outside of India versus in India, or for foreign companies versus domestic companies.

As there is limited guidance available in Schedule Y and the protocol published by the NPP, it is important and useful for the pharmacovigilance team within any pharmaceutical company operating in India to consult the guidance documents available from ICH, the U.S. Food and Drug Administration (FDA) and the European Medicines Agency in their development of well-grounded procedures for pharmacovigilance activities, whether for new or generic drugs.

Clinical Trials Registry

The Clinical Trials Registry – India (CTRI) was set up by the Indian Council of Medical Research's (ICMR's) National Institute of Medical Statistics on July 20, 2007, at the ICMR Headquarters, New Delhi. It has been developed in collaboration with WHO and the Department of Science and Technology. The CTRI is an online database of clinical trials being conducted in India. Any applicant who proposes to conduct a clinical trial in India can register the trial in CTRI prior to enrolling the first participant in its trial. Registration at the CTRI is voluntary and free. The intent behind registering at the CTRI is that it ensures transparency, accountability and accessibility of clinical trials and their results while also streamlining the entire clinical trials process from start to finish. Through the CTRI, information pertaining to clinical trials conducted in India and registered with the database becomes publicly available.[14]

Enforcement and Penalties

As part of outlining Good Manufacturing Practices (GMPs) for pharmaceutical manufacturers in India, Schedule M of the DC Act includes a clause relating to "complaints and adverse reactions"[15] which provides that "Reports of serious adverse drug reactions resulting from the use of a drug along with comments and documents shall be forthwith reported to the concerned licensing authority."[16]

Beyond this, however, the law does not provide any specific information regarding the penalty for noncompliance with its provisions that might be relevant for the purpose of establishing an efficient pharmacovigilance system in India. That said, the DC Act does provide for specific punitive actions against those involved in the sale of spurious or misbranded drugs. They are as follows:

- Penalty for selling spurious drugs likely to cause death or grievous hurt solely on account of their being spurious:
  —Minimum five years imprisonment extendable to a term of life and with a minimum fine of Rs 10,000.

- Penalty for selling other spurious drugs:
  —Minimum five years imprisonment and with a fine which shall not be less than Rs 5000.

- Penalty for selling drugs in contravention of any provision of the Act:
  —Minimum imprisonment of one year.

In addition, there is currently no specific legislation in India that deals with product liability. Because India is a common-law country, reliefs are also available before regulator courts in case of negligence. Reliefs can also be available to consumers of the products under the Consumer Protection Act of 1986 (CPA), wherein a complainant can file a complaint with the appropriate consumer disputes redressal agencies established under the CPA. In personal injury cases, as per practice, the award of damages can be assessed under four main heads: a) special damages in the form of money actually expended; b) cost of future nursing and attendance and medical expenses; c) pain and suffering and loss of amenities; and d) loss of future earnings.

In the interest of strengthening pharmacovigilance standards and performance in India, the government of India organized an "Expert Committee on a Comprehensive Examination of Drug Regulatory Issues, Including the Problem of Spurious Drugs"[17] led by Dr. R.A.

Mashelkar, former director general of the Council of Scientific Research in India. In its interim and final reports, the committee noted that although the DC Act has been in force for more than 50 years, "the level of enforcement in many states has been far from satisfactory."

In tandem with its recommendations that CDSCO "evaluate systematically and scientifically" the "menace of spurious drugs in India," the committee also pushed for certain changes to the DC Act, including "more deterrent measures" for "effective punitive action against manufacturers and distributors of spurious drugs," emphasizing the importance of "'severe' and 'sure' punishment." Among these deterrent measures, according to the committee's recommendations: "the maximum penalty for sale and manufacture of spurious drugs causing grievous hurt or death should be enhanced from life imprisonment to death."[18]

Developing Issues and Future Plans

Generally speaking, pharmacovigilance and issues related to it have yet to receive significant attention and action among many stakeholders and the public at large, even despite the government's nationwide initiatives, including the NPP.

At present, the government has under its consideration the full range of final Mashelkar Committee recommendations. Among those recommendations is the formation of a Central Drug Administration or Authority comparable to FDA. Although the status and composition of such an entity remains under debate, there is broad agreement among government leaders in India that there is an "urgent need for a world-class drugs regulatory system in the country."[19]

Author's Commentary

The Indian market has mostly seen the launch of only those products that have already been approved and marketed in the regulated markets of the United States, Europe, Japan or other countries. In assessing the benefit-risk profile of a drug and to take appropriate corrective actions, Indian pharmaceutical companies and the country's regulatory authorities have been depending on the experiences gained from these markets where the drug was available to consumers for several years before its introduction in India, thus bypassing the requirement to establish a strong pharmacovigilance system of their own.

In recent years, however, many Indian companies have increased their investment in research and development and are enhancing their capacity to develop and market new drugs with their own research efforts. In fact, India is now the fourth largest producer of

pharmaceuticals in the world.[20] Furthermore, India is becoming a major hub for clinical research activities due to its large population and well-defined endogamous subpopulations,[21] high enrollment rates and low costs.

In addition, the lag period between when a drug is placed for the first time on the market in the United States, Europe, Japan or somewhere else in the world and its subsequent availability in India has decreased considerably. As a result for such drugs, the long-term safety data is not available at the time of their marketing in India or is otherwise significantly reduced.[22] In such cases, the Indian regulatory agencies cannot count on the experience of other markets to assess the benefit-risk balance of a drug—a fact that underscores the need to develop and implement an adequately designed pharmacovigilance system in India.

All of these factors have drawn the attention of not only DCGI but also WHO and pharmaceutical companies—all of which have an important role to play in the ultimate functioning of pharmacovigilance activities in India. Indeed, for any pharmacovigilance system to operate well, all stakeholders must be alert and attentive at all stages of a drug's life cycle.

Endnotes

1. More information about the Supreme Court of India is available at http://supremecourtofindia.nic.in/.
2. More information about CDSCO is available at http://cdsco.nic.in.
3. The Drugs and Cosmetics Act of 1940, legislation passed by the Indian parliament, aims to regulate the import, manufacture, distribution and sale of drugs and cosmetics in India.
4. The Drugs and Cosmetics Rules of 1945 have been framed under the Drugs and Cosmetics Act of 1940 and notified by the Department of Health. The DC Rules include various procedural requirements of obtaining, *inter alia*, licenses for the import, manufacture, distribution and sale of drugs and cosmetics, the approvals as required for the conduct of clinical trials, and compliance with the Good Manufacturing Practices regulations.
5. The state agencies do not have any control over granting approvals for clinical trials.
6. Postmarketing surveillance is part of Phase IV of Schedule Y.
7. More information on Schedule Y is available at http://cdsco.nic.in/html/Schedule-Y%20(Amended%20Version-2005)%20original.htm.
8. National Pharmacovigilance Program, *available at* http://www.jipmer.edu/charu/NPVP%20for%20Web.doc.
9. National Pharmacovigilance Protocol, Ministry of Health & Family Welfare, Government of India, *available at* http://cdsco.nic.in/html/Pharmacovigilance%20Protocol%20.pdf.
10. Biswas P, Biswas AK. *Setting standards for proactive pharmacovigilance in India*. 39 Indian J. Pharmacol. 124-8 (2007).
11. Protocol for National Pharmacovigilance Program. CDSCO, Ministry of Health & Family Welfare, Government of India, November 2004.
12. National Pharmacovigilance Protocol, Ministry of Health & Family Welfare, Government of India, *available at* http://cdsco.nic.in/html/Pharmacovigilance%20Protocol%20.pdf.
13. Arora D. *Pharmacovigilance obligations of the pharmaceutical companies in India*. 40 Indian J. Pharmacol. 13-16 (2008). See also the requirement in Schedule Y, *available at* http://cdsco.nic.in/html/Schedule-Y%20(Amended%20Version-2005)%20original.htm.
14. More information about CTRI is available at http://www.ctri.in:8080/Clinicaltrials/trials_jsp/index.jsp.
15. Clause 28.
16. Clause 28.2.
17. The final report of the committee can be accessed at http://cdsco.nic.in/html/Final%20Report%20mashelkar.pdf.
18. Mashelkar Committee report, *available at* http://cdsco.nic.in/html/Final%20Report%20mashelkar.pdf.
19. "Department-Related Parliamentary Standing Committee on Health and Family Welfare, Thirtieth Report on Drugs and Cosmetics (Amendment) Bill-2007," October 2008, *available at* http://www.prsindia.org/docs/bills/1188536330/scr1226998041_Drugs_and_Cosmetics__Amendment__Bill_2007.pdf
20. Biswas et al., *supra* note 10.
21. "Genetic jackpot in India's endogamous gene pool," IndiaInfo.com, June 13, 2005, *available at* http://news.indiainfo.com/2005/06/13/1306genetics.html.
22. Nair MD. Pharmacovigilance: the need for a formal system in India, 2001, *available at* http://www.pharmabiz.com/article/detnews.asp?articleid=11329&sectionid=46.