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BIODESIGN GLOBAL SOURCEBOOK: INDIA REGULATORY BASICS

The Indian government historically has not regulated the country's medical device industry closely. Although this situation has meant easier and faster time to market for new devices in India than in countries with more sophisticated regulatory regimes, it has also undermined public confidence in the country's medical device industry. Since 2008, the government has been working to tighten regulatory control. This chapter introduces readers to India's current regulatory system and reforms.

TOPICS

OBJECTIVES

- ✓ Understand the mission and organization of India's key regulatory body for medical devices.
- ✓ Learn about proposed improvements to the regulatory regime for medical devices.
- ✓ Gain a basic understanding of requirements for registering a device and setting up an acceptable quality system.
- ✓ Become familiar with the process for conducting clinical trials in India.

REGULATORY FUNDAMENTALS

Unlike pharmaceuticals, which have been regulated in India since 1940, the Indian government did not regulate medical devices until very recently. It first proposed regulatory guidelines for

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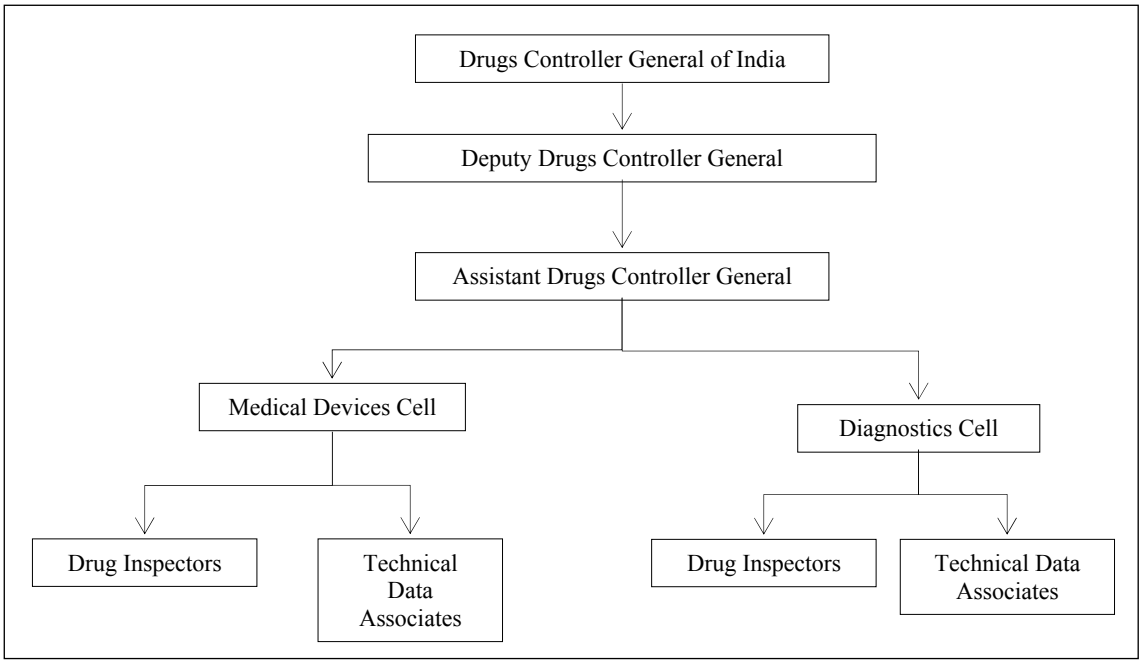
medical devices in 2008, through amendments to the 1940 Drug and Cosmetics Act (DCA). It introduced guidelines on applying drug rules to medical devices in 2012 and will present an updated bill to India's Parliament in late 2013. The new regulations attempt to regulate medical devices as a sector separate from drugs, creating a dedicated control system for device quality, safety, and efficacy.[1]

These efforts will align India more closely with international practice. Regulations touch every stage of the product lifecycle in the global medical devices industry: research and development, clinical trials, premarket approvals, manufacturing, labeling, and ultimately marketing. The Food and Drug Administration (FDA) of the United States and the European CE Marking agencies all regulate medical devices for quality and patient safety under a separate pathway from pharmaceutical drug regulations.

The proposed bill is expected to bring medical devices sold in India under the purview of the government agency charged with regulating medical devices, the Central Licensing Approval Authority (CLAA), which is under the Central Drug Standard Control Organization (CDSCO) under the Ministry of Health and Family Welfare.[2] The New Drugs Division and the Biologicals Division under CDSCO will continue to regulate pharmaceutical drugs.[3]

Until Indian lawmakers approve the new bill, the Medical Device and Diagnostics Division (MDDD) of CDSCO is overseeing the registration of medical devices sold in India and the issuance of import licenses for devices from abroad. MDDD is divided into a Medical Devices group and a Diagnostics group. See Figure 1 for MDDD's organizational structure.[4]

Figure 1: MDDD's organization within CDSCO



Device Classification

Once India's new law goes into effect, the country will start using a device classification system that hews closely to international norms. Based on advice from the World Health Organization, U.S. FDA, the Global Harmonization Task Force, and industry experts, India will classify medical devices into four groups according to their risk level (see Figure 2). In general, it subjects higher risk devices to stricter regulations and a more stringent pre-market conformity assessment process. Medical device manufacturers consequently will need to determine their device's risk classification to ascertain its appropriate regulatory pathway.

Figure 2 Device classification[5]

Europe	U.S.	India	Device Profiles
Class I	Class I	Class A	Non sterile items or sterile items with low potential risk: surgical instruments, urine bags, stethoscopes, examination gloves
Class IIA	Class II	Class B	Sterile items, surgical gloves, urinary catheters, stomach tubes, needles, tracheal tubes, IV giving sets
Class IIB	Class II	Class C	Blood bags, condoms, non-absorbable sutures, anesthesia machines
Class III	Class III	Class D	Active implantable devices, cardiovascular catheters, absorbable sutures, heart valves, collagen implants

In the meantime, CDSCO only regulates 22 device types, requiring their pre-market registration and approval in a prescribed format. These include cardiac stents, bone cements, intra-ocular lenses, orthopedic implants, and heart valves (see Figure 3). They are classified as drugs for the purpose of the DCA and are the subject of notifications in the official *Gazette of India*. Please note that the 22 device types are often referred to as notified devices or devices on the notified list. All other domestically manufactured medical devices can be sold in India without prior registration with the Indian government.

Figure 3: The 22 devices currently regulated by CDSCO[6]

1. Disposable Hypodermic Syringes	7. Catheters	13. Orthopedic Implants	19. Tubal Rings
2. Disposable Hypodermic Needles	8. Intra-Ocular Lenses	14. Internal Prosthetic Replacements	20. Surgical Dressings
3. Disposable Perfusion Sets	9. I.V. Cannulae	15. Blood Group Sera	21. Umbilical Tapes
4. In Vitro Diagnostics Devices for HIV, HCV, and HbsAg	10. Bone Cements	16. Ligatures, Sutures, and Staplers	22. Blood and Blood Component Bags
5. Cardiac Stents	11. Heart Valves	17. Intra-Uterine Devices	
6. Drug-Eluting Stents	12. Scalp Vein Set	18. Condoms	

Device Registration and Licensing

As mentioned above, both domestic and imported medical devices on the notified list require registration prior to sale in India. Under current rules, CDSCO conducts a pre-market conformity assessment review as part of the registration process. Conformity assessments can take six months to one year to complete. Regulators give special treatment to imported notified devices that have already completed regulatory requirements in other countries, which will be explained further below.

Upon its pre-market approval of a domestically produced notified device, CDSCO grants the manufacturer a registration certificate. All domestic manufacturers, whether producing notified or non-notified devices, require a manufacturing license, which they apply for at their local state-level Food and Drug Administration branch under CDSCO. The regulatory agency conducts audits and inspections of manufacturing facilities before granting manufacturing licenses.[7] The CDSCO website[8] maintains a list of licensed indigenous medical device manufacturers.[9]

All firms importing medical devices to India must have an import license, as well as a registration certificate. Imported notified devices can obtain an import license only if they have gone through the registration process and obtained CDSCO's pre-market approval. Medical devices on the notified list that have already obtained regulatory approval in the United States or the European Union can be imported without undergoing separate conformity assessment procedures. They still, however, have to submit the appropriate paperwork to CDSCO to receive a registration certificate and import license.

In brief, there are four main types of submissions that device makers can make to CDSCO: 1) registration of notified medical devices and diagnostics; 2) petition for an import license for the import of medical devices or diagnostics; 3) petition for a test license for the import of small, non-commercial quantities of medical devices or diagnostics for clinical testing;[10] 4) petition for a manufacturing license.[11]

All registrations and licenses are valid for three years from their approval date. Device makers must submit updated paperwork for re-registration of devices or to update expired licenses.[12] See Figure 4 for information about forms and other documents to be submitted to CDSCO for each of these submissions. Forms are available on the CDSCO website, which the agency updated in 2013 to provide several guidance documents on meeting regulatory requirements.[13] These documents can be accessed at http://cdsco.nic.in/Medical_div/medical_device_division.htm and include the following:

- Guidance Document on Application for Grant of License in Form-28 for Manufacture of Medical Devices in India under CLAA Scheme;
- Guidance Document on Common Submission Format for Import License in Form-10 of Notified Medical Devices in India; and
- Guidance Document on Common Submission Format for Registration/ Re-Registration of Notified Medical Devices in India.

Figure 4: Device and diagnostics registration

Submission Type	Forms Needed	Other Documentation
Registration of Notified Medical Devices and Diagnostics	Form 40[14]	• Cover Letter • TR6 Challan (Fees) • Power of Attorney • Free Sale Certificate • Wholesale License (if applicable) • ISO 13485 Certificate (or other quality assurance certificate) • CE Design Certificate (if applicable) • Declaration of Conformity (in case of imported devices) • Plant Master File • Device Master File • Performance Evaluation Report (in case of IVDs)
Import Licenses	Form 10 (includes Forms 8 and 9)[15]	• Cover Letter • TR6 Challan (Fees) • Power of Attorney • Wholesale License / Manufacturing License (as applicable) • Copy of Registration Certificate
Manufacturing License	Form 28[16]	• Cover Letter • TR6 Challan (Fees) • Constitution Details • Manufacturing Premises Plan • Details of Technical Staff • Plant Master File • Device Master File • Product Undertaking by Manufacturer • ISO 13485 Certificate (or other quality assurance certificate) • CE Design Certificate (if applicable) • Declaration of Conformity (in case of imported devices)
Test Licenses	Form 11[17]	• Cover Letter • TR6 Challan (Fees) • Power of Attorney • ISO 13485 Certificate (or other quality assurance certificate)

"New" medical devices on the notified list and in vitro diagnostic products are subject to additional requirements. Fully novel devices that do not have a predicate in the Indian market are considered new medical devices. New notified devices are referred to the Medical Device Advisory Committee of the relevant medical specialty (e.g., Cardiovascular Medicine). These committees advise the Drug Controller General of India on whether to grant permission to new medical devices and clinical trials. Device makers must submit this permission, known as No Objection Certification (NOC), with their other paperwork for device registration. Devices that have a predicate in the Indian market do not have to undergo this procedure.[18] Unlike devices, all in vitro diagnostic products must undergo a performance evaluation in specially designated national labs. Manufacturers submit this report during the registration process.[19]

Quality Management Systems

The proposed regulatory guidelines for medical devices state that CLAA will recognize both BIS 15575 (Bureau of Indian Standards guidelines on medical devices) and ISO 13485 (International Organization for Standardization guidelines on medical device quality management systems) and their revisions. Medical device manufacturers in India will have to demonstrate conformity with these requirements.[20]

CLINICAL TRIALS

Medical device and pharmaceutical drug makers have conducted few clinical trials in India since a January 2013 ruling by the Indian Supreme Court that required the Union Minister for Health to vet every trial personally. The judicial ruling was in response to public interest litigation, which contended that poor regulation of clinical trials involving experimental health products had led to roughly 14,000 adverse effects, including some 2,000 deaths, from 2005-2012.[21] The ruling has mostly affected trials of pharmaceutical drugs, although it has reduced the number of medical device trials as well.

The Indian government first began strengthening supervision of clinical trials in 2009 when the Drug Controller General of India made registration of clinical trials mandatory in India.[22] All clinical trials must now be registered in the Indian Council of Medical Research (ICMR) Clinical Trial Registry, including information about trial investigators, sponsors, enrollment criteria, interventions, endpoints, patient populations, as well as approval from the pertinent ethics committee(s).[23] In January 2013, the Drug Controller General extended registration requirements to ethics committees and institutional review boards. While these steps towards safeguarding patient rights are welcome, the regulatory regime's state of flux has led to delays in new trial approvals and the clinical research industry's contraction.[24]

Given current regulatory uncertainties, medical devices tend to undergo clinical trials only if they are on CDSCO's notified list or the CE Marking process requires clinical data.[25]

Conclusion

Relatively ineffective regulation in India has been a double-edged sword for device manufacturers. It has meant fewer bottlenecks in developing new products and obtaining pre-market approval compared to countries with sophisticated regulatory regimes and more stringent approval criteria. However, this laxity has diminished trust in the efficacy and safety of domestically produced medical products in the eyes of clinicians, their patients, and potential investors. To raise confidence in their products, many device makers subsequently choose to get CE Marking regulatory approval for their products as an indication of device quality. CE Marking is widely accepted in India.

Until the Indian government properly implements and enforces standards across the board, doctors and other professionals making procurement decisions will have trouble determining

which products are truly worth purchasing. The Indian Parliament's expected enactment of the proposed medical devices regulation bill will be an important step in the right direction.

Endnotes

[1] Central Drug Standards Control Organization, "Medical Devices," http://cdsco.nic.in/Medical_div/medical_device_division.htm (February 22, 2013).
[2] "Schedule M III: Medical Devices Guidelines," CDSCO Final Draft, February 23, 2009, p.8, http://cdsco.nic.in/Medical_Devices_Guidelines.pdf (August 1, 2013).
[3] Central Drug Standards Control Organization, "Divisions," http://www.cdsco.nic.in/ (July 20, 2013).
[4] "Organogram of the Medical Device Division," CDSCO, http://cdsco.nic.in/Organogram%20of%20Medical%20Device1.pdf (August 1, 2013).
[5] Ibid.
[6] "List of Notified Medical Devices," CDSCO, http://cdsco.nic.in/Medical_div/list%20of%20notified%20medical%20device.0001.pdf (July 20, 2013).
[7] "Guidance Document on Grant of Manufacturing License," CDSCO January 1, 2013, p. 16, http://cdsco.nic.in/Medical_div/Final%20Guidance_Doc_Form-28_31-10-2012.pdf (July 31, 2013).
[8] CDSCO, http://www.cdsco.nic.in/ (September 10, 2013).
[9] "Schedule M III: Medical Devices Guidelines," loc. cit.
[10] "Frequently Asked Questions on Registration and Import of Medical Devices in India," CDSCO, pp. 2, 3, and 6. http://cdsco.nic.in/FAQ-IMPORT%20&%20REGISTRATION%2002022013_DONEE.pdf (July 29, 2013).
[11] "Guidance Document on Grant of Manufacturing License," op. cit., p. 2.
[12] "Frequently Asked Questions on Registration and Import of Medical Devices in India," p. 5.
[13] Ibid., p.1.
[14] Ibid.
[15] "Draft List of Documents to be Submitted for Import License Form 10," CDSCO, http://cdsco.nic.in/CHECKLIST%20FOR%20THE%20GRANT%20OF%20FORM%2010%20LICENSE%20FOR%20THE%20IMPORT%20OF%20NON-CRITICAL%20DIAGNOSTIC%20KITS.htm (July 31, 2013).
[16] "Guidance Document on Grant of Manufacturing License," loc. cit.
[17] "Frequently Asked Questions on Registration and Import of Medical Devices in India," p. 6.
[18] Ibid., p. 8.
[19] "Frequently Asked Questions on Registration of In Vitro Diagnostic Devices (IVDs)," CDSCO, February 21, 2013, pp. 8-11, http://cdsco.nic.in/Final%20FAQS-IVD.pdf (July 31, 2013).
[20] "Schedule MIII: Medical Devices Guidelines," loc. cit.
[21] Vidya Krishnan, "Government Approves 50 Clinical Trials," *LiveMint*, July 2, 2013, http://www.livemint.com/Politics/3qKJFsCnZHKreKE81fheEP/Government-approves-50-clinical-trials.html (July 15, 2013).
[22] "Advisory Notice on Clinical Trials," CDSCO, http://www.cdsco.nic.in/clinical_trial.htm (July 15, 2013).
[23] "Clinical Trial Registry – India," http://ctri.nic.in/Clinicaltrials/login.php (July 15, 2013).
[24] Vidya Krishnan and Jacob Koshy, "US Agency NIH Scraps Nearly 40 Trials in India," *LiveMint,* July 11, 2013, http://www.livemint.com/Politics/zwG7cCA7nFYFdpzYLXcCVM/US-agency-NIH-cancels-nearly-40-ongoing-clinical-trials-in-I.html (July 15, 2013).
[25] "CE Mark: A Guide for Medical Device Companies," MDT International, Issue CE 11, pp. 5-6, http://mdtinternational.eu/mdt/Docs/CE%20Mark%20-%20Issue%20CE11.pdf (July 31, 2013).