The Indian pharmaceutical environment

Introduction
At the start of the last century the pharmaceutical industry was practically non-existent in India, and pharmaceuticals were imported from abroad. Following the First World War, this situation changed, and not only were pharmaceutical products imported in increasing volume, but the demand for indigenous products also grew. This led to a rapid expansion of pharmaceutical production during the early part of the century, and it became clear that comprehensive legislation was needed. Because of this, the Indian government passed the Drugs Act in 1940.

Several different factors have increased India’s attractiveness as a destination for the pharmaceutical industry. These range from changes in the laws related to intellectual property, drug registration and patent protection to favourable cost/skill ratios, which together have seen India become a compelling business opportunity.

All regulatory aspects related to the manufacture, sale, import, export and clinical research of drugs and cosmetics in India are covered under the following Acts and Rules: The Drugs and Cosmetics Act 1940 (D and C Act); The Pharmacy Act 1948; The Drugs and Magic Remedies (Objectionable Advertisements) Act 1954; The Narcotic Drugs and Psychotropic Substances Act, 1985; The Medicinal and Toilet Preparations (D and C Act); The Pharmacy Act 1948; The Medicinal and Toilet Preparations (Excise Duties) Act 1956, and The Drugs (Prices Control) Order 1995 (under the Essential Commodities Act).

The regulatory system
India has a federal form of government and the medical regulatory structure is divided between national and state authorities. The principal national drug authority based in New Delhi is the Central Drug Standards Control Organization (CDSCO). CDSCO is controlled by the Drug Controller General India (DCGI).

There are also 35 state-level Food and Drug Administrations, one for each of India’s states and territories.

The DCGI registers all imported drugs, new drugs, biologicals and drugs in selected categories. It also has responsibility for medical devices, clinical trials and quality standards. The drug regulatory system structure is shown in Figure 1.

The state FDAs register all other products, accredit manufacturing plants, and conduct the bulk of quality monitoring and inspections.

Classification of drugs
D and C Act 1940 has listed drugs in Schedules. Prescription-only medicines are listed in Schedules H and X. Drugs listed in Schedule G (mostly antihistamines) do not need a prescription to purchase but require the following mandatory text on the label: ‘Caution: It is dangerous to take this preparation except under medical supervision.’

Drugs falling in the above three schedules are currently not advertised to the public under a voluntary commitment by the pharmaceutical industry.

All medicinal products that are not included in the list of ‘prescription-only drugs’ are considered as non-prescription drugs (OTC, or over the counter) in India, though the phrase ‘OTC drugs’ has no legal recognition.

Regulatory approval timelines are detailed in Table 1.

Registration of imported drugs
All drugs to be imported require their own import registration. This is independent of new the required drug registrations. Foreign manufacturers must apply for registration certification for their manufacturing premises and for the individual drugs to be imported. Applications can be made by authorised agents of foreign firms in India.

According to recent new legislation, import licences will be required for all types of drugs, rather than the existing import licence requirements for Schedule C and C (I) and Schedule X drugs only.

Import licence applications should be made using Form 40, and information and undertakings specified in Schedule D(I) and Schedule D(III) should duly signed by the manufacturer.

Schedule D(I) and D(III) should comprise actual plant and drug data, such as the plant master file; the manufacturing licence in country of origin; a GMP certificate; a Certificate of Pharmaceutical Products (CPP) issued by the regulatory authority of the country of origin; drug substance information; finished formulation information; clinical documentation, and packaging and labelling information.

The process of receiving import registration can take up to 12 months. Once you have import registration (valid for three years) for a drug, you can apply for a simple import licence via Form 8 or Form 8A, which is needed for customs clearance.
**Figure 1: India’s drug regulatory system**

- NATIONAL GOVERNMENT
  - MINISTRY OF HEALTH and FAMILY WELFARE
  - MINISTRY OF ENVIRONMENT
  - MINISTRY OF CHEMICALS and PETROCHEMICALS

- Central Drugs Standard Control Organisation (CDSCO)
- Genetic Engineering Approval Council (GEAC)
- NPPA – National Pharmaceutical Pricing Authority
- DCP – Department of Chemicals & Petrochemicals

**Figure 2: India’s clinical trial process for pharmaceutical products and medical devices**

1. **Parallel submission to Ethics Committee**
   - Category A: Clinical trial already approved by other regulatory agencies and approval letters available
   - Application made to DCGI for approval in Form 44 and import licence in Form 12. Fees Paid
   - Application evaluated for completeness and, if found appropriate, approval normally granted in 4-6 weeks
   - Approved NOC received from DCGI
   - If rejected, resubmit application
   - Export licence received within 2 weeks

2. **Category B: Clinical trial not approved**
   - Application made to DCGI for approval in Form 44 and import licence in Form 12. Fees Paid
   - Application evaluated for completeness and, if found appropriate, approval normally granted in 8-12 weeks
   - Apply to Joint DGFT of the respective city/state with cover letter and NOC from DGFT
   - Approval received within 4-6 weeks

**Figure 3: Current and predicted growth of the pharmaceutical industry in India**

<table>
<thead>
<tr>
<th>Year</th>
<th>Sales, €bn</th>
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<tbody>
<tr>
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<td>2014</td>
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Source: www.dbresearch.com accessed 8 December, 2009

**New drug registration**

Medicinal products count as ‘new drugs’ in India if they fall into one of the following categories:
- Drugs not previously available on the market in India
- Drugs with new therapeutic indications or dosages that have not been marketed in India
- New fixed-dose combinations of two or more drugs
- Any drug which was first approved in India less than four years ago, unless it is included in the Indian Pharmacopoeia
- All vaccines are treated as new drugs, unless notified otherwise by the DCGI.

New drug registration is applied for via Form 44, and information should be submitted as per Schedule Y format.

Schedule Y covers information such as basic dosage and indication data, active and inactive data, patents information (if any exist), regulatory status in other countries, and marketing information.

The required attachments to the form vary depending on the type of new drug.

New drug registration carries a fee of 50,000 rupees. There is no fixed timeframe in which the application has to be reviewed, but a typical range is around 12-18 months.

**Registration for a medical device**

CDSCO regulates medical devices registration and import. The health ministry in 2005 declared the following sterile devices to be considered as drugs: cardiac stents; drug eluting stents; catheters; intra-ocular lenses; intravenous cannulae; bone cements; heart valves; scalp vein sets; orthopaedic implants; internal prosthetic replacements. Various other sterile medical devices such as spinal needles, insulin syringes, cardiac patches and many others were added to this category in March 2009.

Registration applications should be submitted via Form 40 and as under Rule 24A of the Drugs and Cosmetics Rules. The product information and undertakings should be submitted under Schedule D(I) and D(II) – these schedules are modified to suit the requirements of devices, such as category of device, intended use and method of use, qualitative and quantitative particulars of the constituents, contraindications, lists of accessories. Details of the clinical trial process for pharmaceuticals and medical devices are given in Figure 2.
Application and approval procedures for clinical trials

Clinical trials are applied for via Form 44, the same form used for new drug approvals. Data should be submitted along with the application in Schedule Y of the Drugs and Cosmetics Act 1940, and the rules therein.

CDSCO decided to make registration of clinical trials in the Indian Council of Medical Research (ICMR) clinical trial registry mandatory in June 2009, applicable for clinical trials initiated after 15 June 2009 (for more details, see www.ctri.in).

Registration for biological drugs

For biologicals, along with DCGI approval, additional approvals have been required by other offices and agencies, including the Genetic Engineering Approval Council (GEAC); Recombinant DNA Advisory Committee (RDAC); Review Committee on Genetic Manipulation (RCGM); Institutional Biosafety Committees (IBSC); State Biosafety Coordination Committees (SBCC); and the District Level Committees (DLC).

Recently, CDSCO has issued guidelines for clinical trials (Document No CT/71108, version 1.1) and for the marketing authorisation of biological products (Document No MA/71108, version 1.1). The requirements in respect of chemistry and pharmaceutical information have been elaborated in CTD format while requirements for nonclinical and clinical trials remain the same as per schedule Y of the Drug and Cosmetics Rules 1945. Post-approval changes in biological products are covered in the guideline document No PAC/1108, version 1.1.

Industry developments – patents

The Indian parliament approved India’s product patent legislation in March 2005. The Indian Patents Third Amendment Bill, 2005, establishes product patent protection for pharmaceuticals in India. Manufacturers of new drugs can apply for product patents. With the patents regulations now in place, the Indian government can process ‘mailbox’ patent applications.

The mandatory compulsory licensing for ‘mailbox’ patents will not permit patent holders to eliminate generic copies that are present in the Indian market prior to January 1, 2005. In such a situation, the patent holder will only be entitled to receive a reasonable royalty.

The manual on patent practice and procedures in India is a detailed document, available on the website: http://www.patentoffice.nic.in/ipr/patent/patents.htm.

Industry developments – the pharmacovigilance system

The current national pharmacovigilance system came into effect in 2005. The importance of post-marketing surveillance by the regulatory authorities has also been reiterated by a number of high-level committees. The task ahead is enforcement of this system across the nation.

India’s pharma industry growth

India gained its foothold on the global scene with generic drugs and active pharmaceutical ingredients, and it is now seeking to become a major player in outsourced clinical research, medical writing, contract manufacturing and research. Between 1996 and 2006, nominal sales of pharmaceuticals were up 9% per annum, thus expanding much faster than the global pharmaceutical market as a whole (+7% per annum). Demand in India is growing rapidly, due to rising population numbers, the increasing number of elderly people and the growth in incomes of India’s population as a whole. As a manufacturing location, the country is benefiting from its wage-cost advantages over Western competitors, which is also true in terms of developing medicinal products.

It is predicted that until 2015, pharmaceutical sales are expected to rise by 8% per annum, to around €20 billion (see Figure 3), compared with an expected increase of 6% in other key markets. In terms of scale, the Indian pharmaceutical market is ranked 14th in the world. By 2015, it is predicted to rank among the top ten, overtaking Brazil, Mexico, South Korea and Turkey.

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