India

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The drug regulatory scenario in India is monitored by the Drugs Controller General India (DCGI) who is supported by various other bodies from the Ministry of Health (MOH) such as the Drugs Consultative Committee and Drugs Technical Advisory Board, as well as the commissioners of the Food and Drug Administration offices which are operational in the various states of India. DCGI is under the auspices of the Directorate General of Health Services under the MOH and is located in New Delhi, the capital of India.

REGULATORY LAWS

The main regulatory laws operating in India are the Drugs and Cosmetics Act 1940, Drugs and Cosmetics Rules 1945, Drugs and Magic Remedies (objectionable advertisements) Act 1954, Narcotics and Psychotropic Substances Act 1985, Drugs (Prices control) Order 1995. Various other laws support the regulation of import, manufacture, pricing, distribution and sale of drugs. A Central Drug Laboratory has also been established in Calcutta to monitor the quality of drugs under the supervision of the government analyst. Although the Act and Rules date from some time ago, they are periodically updated and amendments to the existing Act/Rule are issued. Whenever an amendment is to be issued, the draft is sent out by the government for comments within a specified time frame and the finalised document is then put before the parliament for approval as law. The amendment is then published in a Government of India Gazette Notification and then becomes a law. The Act and Rules are binding on allopathic and other systems of medicine such as ayurvedic, homoeopathic, siddha, unani for human and veterinary use as well as cosmetics.

SCHEDULES

The Rules contain various schedules which are interlinked. There are schedules covering almost the entire alphabetical range. Schedule A lists the various application/approval forms pertaining to different activities of manufacture, sale and import; Schedule H lists the drugs to be sold by prescription; Schedule K lists home remedies; Schedule M lists the good manufacturing practice (GMP) requirements; Schedule X lists the psychotropic drugs which have special controls; Schedule Y lists the requirements and guidelines for the import and manufacture of a new drug; Table 1 lists the various schedules. Registration of new drugs in India is governed by Schedule Y. The objective of this article is to outline the registration process in India. Hence, the focus would be on Schedule Y. The various schedules and rules are interlinked. For example, Schedule H, which lists prescription drugs, is linked to Rules 65 and 97 on conditions of licence and requirements of labelling of such drugs.

Table 1. Schedules to the Act and Rules.

Schedule	Applications
A	Applications/licences for import, manufacture, stock, sale, etc. of drugs/cosmetics with allied matters pertaining to drug regulation
B	Fees for tests/analysis to government laboratories
C	Biological/immunological/ophthalmologic products, antibiotics and all products for parenteral use
C1	Alkaloids, hormones, vitamins, antibiotics for oral use
D	Conditions of exemption granted to certain drugs and importers of drugs
E	Deleted in 1982; nonexistent now but contained list of poisons
E1	Poisonous substances under alternative systems of medicine such as ayurveda, siddha and unani
F	Requirements of blood banks; provisions of manufacturing/testing/labelling of biological products for human use (e.g., sera, vaccines)
F1	Manufacture/testing/labelling of vaccines, antisera and diagnostic antigens
F2	Standards for surgical dressings
F3	Standards for umbilical tapes
FF	Additional standards for ophthalmic preparations
G	Drugs to be used under medical supervision
H	Prescription drugs
I	Deleted 1982; nonexistent now and linked to Schedule E

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J	Names of diseases/ailments by whatever name which a drug may not purport to prevent/cure or make claims to prevent/cure
K	Conditions where drugs or classes of drugs are exempt from provisions of manufacture/sale; lists 'home remedies'
L	Deleted in 1982; nonexistent now and contained certain prescription drugs which are now transferred to Schedule H
M	GMP requirements of premises, plant and equipment
N	Requirements for running a pharmacy
O	Standards for disinfectant fluids
P	Shelf life and conditions for storage of drugs
P1	Pack sizes of drugs
Q	Dye, colours and pigments permitted to be used in cosmetics and soaps
R	Standards and labelling requirements of condoms
S	Standards for cosmetics
T	Requirements of factory premises for ayurvedic/siddha/unani drugs
U	Maintenance of manufacturing and analytical records
V	Standards for patent and proprietary medicines and permissible range of vitamins in preparations for oral use
W	Drugs to be marketed by generic names only
X	Psychotropic drugs list
Y	Requirements and guidelines on clinical trials for import/manufacture of 'new' drugs

REGISTRATION OF NEW DRUGS

Schedule Y was enacted as per the Government of India notification of 21 September 1988. A new drug can be imported and marketed in India under Rule 122A; a new active substance can be imported under Rule 122A for the manufacture of the formulation under Rule 122B/C; a new formulation can be manufactured and marketed under Rule 122B (drugs other than those classified Schedule C and C1); a new formulation can be manufactured and marketed under Rule 122C (drugs classified as Schedule C and C1); fixed dose combination preparations are regulated by Rule 122D.

Rule 122E defines a 'new' drug as one which includes:

- a new substance of chemical, biological, recombinant biotechnological origin or such devices or delivery systems in bulk or prepared dosage form intended for internal or external use in the diagnosis, prevention, treatment or mitigation of disorders in human beings or animals (It may

also include such substances other than food intended to affect the structure of the human body and also those substances intended to be used as components of drugs), which, except during local clinical trials, has not been used in the country to any significant extent, and except during local clinical trials has not been recognised in the country as effective and safe for the proposed claim;

- a drug already approved for certain claims which is now proposed to be marketed with modified or new claims, namely, indications, dosage, dosage forms (including sustained release forms) and route of administration;

- a fixed dose combination of two or more drugs individually approved earlier for certain claims that are now proposed to be combined for the first time in a fixed dose ratio, or if the ratio of an already marketed combination is proposed to be changed with certain claims.

Above and beyond these definitions, all vaccines would be considered as new unless certified otherwise by the DCGI.

FOUR-YEAR STIPULATION

It is interesting to note that a 'new' drug would be considered as 'new' for a period of four years from the date of its first approval or its inclusion in the Indian *Pharmacopoeia*, whichever is earlier. This four-year stipulation means that all subsequent entrants for a specific 'new' drug would need to obtain the approval of the DCGI. Once the four-year limit is crossed or the drug is included in the Indian *Pharmacopoeia*, a drug can be introduced after obtaining the necessary licence from the local state Food and Drug Commissioner office. It may be noted that even after getting the approval of the DCGI, one has to obtain the requisite licence from the local state Food and Drugs Administration office before marketing the drug.

REQUIREMENTS FOR REGISTRATION

Clinical Trial Requirements

The need for local clinical trials in India prior to approval of the drug depends on the status of the drug in other countries. If the drug is already marketed elsewhere, Phase III trials are usually required; if not marketed elsewhere, generally trials one phase earlier to the phase in other countries are required to be conducted. For new drugs discovered in other countries, Phase I trials are usually not allowed in India unless Phase I data in other countries are available. The DCGI may, however, permit such trials if the drug is of special relevance to a health problem in India (e.g., malaria, tuberculosis). For new drugs discovered in India, clinical trials from Phase I to III are required and trial permissions are granted in stages depending on the data emerging from the previous phases.

Permissions for Conducting Clinical Trials

No new drug clinical trial can be carried out without the permission of the DCGI. Data appropriate to the phase of the trial along with the proposed protocol, case record form, names of investigators and centres have to be submitted for approval. The investigator has to have appropriate facilities and expertise and the trial is usually required to be carried out in teaching medical institutions. Protocols are to be reviewed and approved by the ethical committee of the institution. However, if an institution does not have an ethical committee, approval by the DCGI is adequate to initiate the trial. Clinical trials in children may be permitted only after the Phase III trials in adults are completed; however, if a drug has value primarily in diseases of children, early paediatric trials may be allowed.

Responsibilities of the Investigator/Sponsor

Informed consent has to be obtained in the prescribed format. An annual status report must be done on current patients and those who have been terminated, with reasons for termination. Any unusual, unexpected or serious adverse reactions are required to be communicated.

Contents of the Registration Dossier

The registration dossier must contain the following:

- Introduction: a brief description of the overall properties, actions, indications, efficacy and tolerability.
- Chemical and pharmaceutical documents: chemical name, composition, specifications, analytical methods, outline of method of manufacture and stability data.
- Preclinical data:
    - Animal pharmacology: a summary along with specific and general pharmacological actions and pharmacokinetic data.
    - Animal toxicology: a summary along with acute, long-term, reproduction, local toxicity and mutagenic/carcinogenic data. There are detailed requirements of toxicity studies in terms of time, dose, route of administration, which are beyond the scope of this article. Reproduction study requirements are also specified in terms of fertility studies, teratogenecity studies and perinatal studies. Local toxicity is limited to preparations intended for topical use.

- Clinical data:
  - Phase I studies are required to be carried out in 1 to 2 centres adequately equipped for clinical pharmacology studies. At least 2 adult male volunteers are to be tested for each dose.
  - Phase II studies are to be carried out at 3 to 4 centres by clinicians specialised in the particular therapeutic area of the drug being tested and normally 10 to 12 patients are to be tested at each dose level.
  - Phase III studies are required to be conducted by clinicians in the concerned therapeutic area and generally in comparison to a standard drug or placebo as appropriate. Data in at least 100 patients are required if the drug is marketed in other countries; data in at least 500 patients distributed in 10 to 15 centres are needed if the drug is a new entity discovered in India and not marketed in any other country. In addition, data from clinicians on adverse drug reactions observed during clinical use in about 1,000 to 2,000 patients are required to be submitted.
- Special studies: Special studies include bioavailability/bioequivalence studies or in vitro dissolution studies where data on formulations manufactured in the country need to be given. Data to explore the effects in the elderly or in patients with renal failure or expected drug interactions are to be provided as appropriate.

Clinical Trials Report

A prescribed format is given including among other things, the objectives, design, patients, treatments, observations before/after, results, discussions and summary/conclusions.

Regulatory Status in Other Countries

A list of countries where registered/marketed and withdrawn/restricted use giving reasons thereof is required to be forwarded.

Marketing Information

The detailed product monograph giving description, actions, indications, dosage, administration, warnings, precautions, interactions and adverse reactions is to be forwarded together with the layout of the proposed label and carton texts.

REGULATORY ENVIRONMENT AND PRACTICES

Having given an overview of the requirements, we now outline some practical issues:

- Registration of the drug in the country of origin and its status in the United Kingdom and United States of America play an important role in the local registration review.
- It is not necessary for all applicants to conduct clinical trials if deemed so by the DCGI. Subsequent applicants may be required to conduct bioavailability studies and in vitro dissolution studies to further their application. Registration is not necessarily granted first to the first applicant; if a subsequent applicant has successfully carried out trials and bioavailability studies and has submitted the data before the first applicant, and the DCGI finds this data adequate, then registration can be granted to the subsequent applicant before the first applicant.
- Bioequivalence studies are required to be conducted in 12 healthy male volunteers after getting the protocol and centre duly approved by the DCGI. The product being tested is to be compared to the innovator formulation.
- Certain drugs which are specific to special disease areas (e.g., anti-cancer) or novel delivery systems (e.g., transdermal therapeutic systems) may be referred by the DCGI for experts' opinion and the product may be cleared based on experts' opinion. Such an approval procedure may be considered by the DCGI, based on the medical need and desirability of the product in India. The DCGI selects a list of experts in the field and technical/medical literature is forwarded to the experts who give their feedback directly to the DCGI.
- Drugs of biotechnological origin would need the approval of the Biotechnology Board in addition to the approval by the DCGI. The DCGI would forward the application for the Board's opinion.
- Conduct of Post-marketing Surveillance study (PMS) is a regulatory stipulation. Usually the protocol and centres need to have an approval of the DCGI before initiation of the PMS study.
- Permission is granted in the generic name along with the approved strengths. As per the current regulatory scenario, generic names are required to be labelled double the size of the trade name. The trade name would appear either below or after the trade name and both names would be in the same type and colour scheme.
- If a drug is permitted for manufacture and for a justified reason, a company cannot manufacture the same drug for some time and if there is a medical need, the DCGI may consider granting the import of a specified

quantity of the drug as one-time import to tide over the medical need. This procedure is more an exception than a rule and is granted only occasionally for a convincing rationale.

- Clinical trials can be done on imported formulations; should the application be to import and market, then these studies are acceptable for registration. However, if the application is to manufacture and market, the company would need to formulate the local product and perform bioequivalence studies to the imported formulation. In all likelihood, no trials would need to be conducted with the local formulation. The company can import the active substance to make the local formulation.
- The first batch of the active substance needs the approval of the Central Drug Laboratory in Calcutta before it is used for the manufacture of the formulation locally. Likewise, the first batch of the imported formulation has to be approved by the same laboratory before marketing.
- The DCGI has currently been issuing time-bound permissions for two years only. Revalidation of the permission is dependent on conducting the stipulated PMS study and submission of the data to the DCGI.
- After the approval by the DCGI, the company would need to obtain the manufacturing licence from the concerned local state FDA office. The technical documents on the product as well as administrative/technical documents on the premises need to be furnished in this case.

MANUFACTURING OPTIONS

A company can manufacture the drug at its own premises with its own licence. It can also get the drug manufactured at another manufacturing site by loaning licence. Such a practice is called 'loan-licence manufacture'. Drugs can also be manufactured on a principal-to-principal basis whereby drugs manufactured at approved premises on their licence can be marketed by another company. Many factors govern such operational options, for example, technical feasibility, financial considerations and so on. The granting of a manufacturing licence implies compliance to Schedule M, which means that GMP are followed as per the Act and Rules.

CURRENT DEVELOPMENTS

Guidelines for Bioavailability/Bioequivalence Studies

Bioavailability and bioequivalence study guidelines are being developed jointly in consultation with academia and industry. The guidelines have undergone a draft stage and are under review.

Over-the-Counter (OTC) Guidelines

There is no official OTC status for drugs in India. However, there is a classification of drugs termed as 'home remedies' under Schedule K, such as paracetamol, aspirin, cough and cold preparations, rubs, liniments and the like, which can be stocked and marketed as per said provisions under Schedule K and rules thereof. As there is no official OTC status, drugs (other than those in Schedule K) cannot be advertised in the lay media. Guidelines are under preparation for establishing OTC drugs as well as prescription to OTC switch policy.

Marketing Communication Policy (MCP) Guidelines

In consultation with the industry, marketing communication policy guidelines are being drawn which are in line with the International Federation of Pharmaceutical Manufacturers Association (IFPMA) code.

Good Clinical Practice (GCP) Guidelines

The draft of GCP guidelines has been prepared in consultation with the industry and is likely to be appended to Schedule Y.

Investigational New Drug (IND) Format

In the offing are the IND format requirements which must be complied with before clinical trials are initiated. The sponsors are required to provide details in a specified format to the DCGI comprising the generic name, patent status, brief description of physico-chemical/biological parameters and technical information such as stability, specifications, manufacturing process, worldwide regulatory status, animal pharmacology and toxicity studies, published clinical trial reports, proposed protocol and proforma, trial duration, drug master file, undertaking to report serious or life-threatening adverse drug reactions. There are administrative requirements for providing the above information as per specified colour-coded sections (as detailed in the IND format). A presentation of the data has to be additionally made to the DCGI officials before the clinical trial permission is granted.

ADVERTISEMENT OF DRUGS

Drugs and Magic Remedies Act and Rules govern the advertisement of drugs. Medical information is primarily meant for the 'use of registered medical practitioners or a hospital or a laboratory' and companies are not permitted to give medical information directly to consumers. Advertisements in medical journals are in practice, however, and the ethical companies include the abridged prescribing information. The portion in quote is to be printed on the package insert. Of late, companies have started issuing patient package inserts for some products.

The Act and Rules therefore control the advertisement of drugs and in certain cases prohibit the advertisement of remedies alleged to possess magic qualities and for which specified diseases and disorders are given in the said schedule. For example, it is prohibited to advertise drugs for the maintenance or improvement of the capacity of human beings for sexual pleasure.

Model guidelines on Code of Ethics for advertisement of drugs have been issued by the subcommittee on the code of ethics for advertisement of drugs. The objective of the code is to ensure responsible advertising in promoting the sale of medicines which may be purchased by the public without prescription and for which therapeutic claims are made. Some of the general principles to be followed are the stipulation that these advertisements not be offensive, misleading or derogatory to competitive products, offer rewards for use, give an impression that a medical consultation is unnecessary, including prescription drugs, imply that it is recommended by health professionals, and so on.

PRICING OF DRUGS

The Drugs (Prices Control Order) 1995 controls the procedure for working out the pricing in the ultimate interest of the consumers and manufacturers. This order provides for fixing of ceiling prices for commonly used packs of formulations based on price controlled drugs. These prices would be applicable to all manufacturers. There are certain exemptions for small-scale manufacturing units, drugs produced with indigenous research and development and so on. The order lists drugs with price control of 100 percent for maximum allowable post-marketing expenses.

OTHER LAWS

Briefly mentioned are other laws which govern the different aspects of pharmaceutical operations; the basic laws are amended from time to time.

- The Industries (Development and Regulation) Act 1951 provides for development and regulation of various industries including pharmaceuticals and cosmetics.
- The Trade and Merchandise Act 1958 provides for registration and better protection of trademarks and for the prevention of fraudulent use of trademarks.
- The Indian Patents and Design Act 1970 protects inventions and designs. This is updated and the Patents Bill has been recently passed. The amendments have a Mail Box provision with a right to claim Exclusive Marketing Rights (EMRs) for patents filed after 1 January 1995, subject to certain conditions. These transitional arrangements are the beginning of an anticipated full amendment of the patent law by 1 January, 2005.

- The Poisons Act of 1919 consolidates the laws regulating importation, possession and sale of poisons. Specific permits are needed and substances are classified as poisons as per scheduled list.
- The Narcotic and Psychotropic Substances Act 1985 controls the regulation of substances specified as narcotics and psychotropic substances. In addition to the DCGI, the Narcotics Commissioner in Gwalior, India controls the various operations pertaining to such substances.
- The Pharmacy Act of 1948 governs the overall pharmacy profession in India. A Central Pharmacy Council of India and State Pharmacy Councils are established with stipulated membership on the governing bodies.

CONCLUSION

On perusal of the above scenario, one could surmise that the operations in India are quite up to the standards of developed countries. The vast multitude in India with a varied cross section of habits, cultures, diversity of languages, medical practices and operational systems, literacy levels, local and multinational players, small scale and large scale units, clandestine parallel imports and so on, make the task of monitoring the regulation of the rules and operations a real challenge. In order to have a facilitated registration in the Asia-Pacific region, it would be desirable to have a Mutual Recognition Procedure along the lines of that for the European Union.

REFERENCES

Gazette of India. No. 505 (21 Sep. 1988) pp. 10–19.

Dutta, P. K., ed. 1997. *Drug Control—Desk Reference.* Eastern Law House, Calcutta, India.

Mehra, M. L., ed. 1997. *Handbook of Drug Laws*. University Book Agency, Allahabad, India.

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