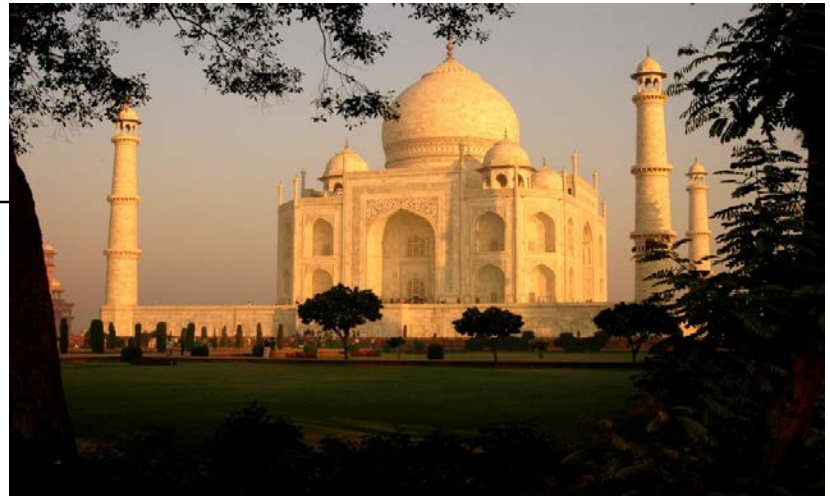
Update on India's Medical Device Markets

June 9, 2009



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PBM's Partner in India

India's Demographics – Overview

- Population : 1.130 billion
- Rural / urban population : 70% / 30%
- Birth rate : 2.3%
- Mortality rate : 0.7%
- Life expectancy (years) : 66 (M) / 71 (F)
- Population profile (years):
  - < 15 / 15-64 / >64 : 32% / 63% / 5%
- Literacy rate : 65%
- Unemployment rate: : 8%

India – Healthcare

- Expenditure on healthcare including services, medical devices and pharmaceuticals is US $35 billion, 4% of GDP.
- Public sector share of spend is 25% and insurance, corporate, individuals spend 75%
- Healthcare delivery market has recently grown at 13% per year and is expected to grow at 15% per year over the next 5 years.

India's Healthcare System

- Hospitals (Government and private): 16,000, Beds, > 1,000,000
- Government Primary Health Centers (4-6 beds): 23,000
- Government Community Health Centers (30 beds) : 4000
- Diagnostic clinics: 16,000

Healthcare Growth Drivers

- Government's National Health Policy envisages increase in healthcare spending to 6% of GDP by 2010.
- Government initiatives such as the National Healthcare Mission, World Bank funded projects, specific disease eradication projects.
- Projected increase in healthcare insurance.

India – Disease profile

- Malaria : 2.2 million per year
- Leprosy : 0.5 million
- Diabetes : 40 million
- Asthma : 40 million
- Cancer : 3 million
- HIV/AIDS : 10 million
- Tuberculosis : 14 million
- Cataract : 3.8 million per year
- Other significant diseases are in the areas of cardiology, respiratory, water-borne and other infections, gastroenterology, orthopedic, nephrology, urology.

India – Market Characteristics

- Quality of service in private sector is good.
- Government sector is low on quality and availability – patients prefer private treatment.
- 65% of healthcare costs are borne directly by patients.

Healthcare Comparative Costs

Procedure	Cost in India (US $)	Cost in USA (US $)
Heart surgery	6,000	24,000
Bone marrow transplant	30,000	250,000
Liver transplant	40,000	300,000
Neurosurgery	8,000	29,000
Orthopedic surgery	6,000	20,000
Cosmetic surgery	2,000	20,000

Insurance & Reimbursement

- There is no single national health insurance system.
- What exists is a number of schemes of free/concessional treatments and insurance, mainly for hospitalization.
- Medicines, devices and services are provided/reimbursed within the applicable cost limits.

Healthcare Coverage

- The Central Government Health Scheme (CGHS) provides free/concessional treatment in Government and other approved hospitals for about 4.5 million government employees and retirees and their families. They have 244 clinics of their own and also use referral hospitals..
- The Employees State Insurance Scheme (contributory but mandatory for lower-paid employees) covers around 0.5 million non-government employees. The system has 144 hospitals and 1422 dispensaries.
- The Railways Health Scheme (121 hospitals and 586 clinics) covers 1.2 million railway employees and families.

Health Insurance

- Health Insurance is relatively new and is provided by both Government insurers and foreign-Indian joint ventures.
- 30 million people are covered, and expected to grow to 150 million by 2012.

India's Medical Device Market (1)

- Market size: US$2.5 billion
- Per capita spending: US$2.50
- Imports: 75%
- Recent annual growth rate: 6%
- Projected growth rate up to 2010: 12 – 16%

India's Medical Device Market (2)

- Local non-multinational medical manufacturers are small, low tech, generally low cost, and medium quality: some are FDA/CE approved.
- Multinational medical companies also manufacture/import into India.

Growth Drivers for Device Market

- High projected demand based on:
- Multinationals have been able to realize prices which are remunerative and also affordable to customers.
- As of now, there are **no** mandatory price controls for devices.
- Currently, there is not much regulation but this is beginning to change.

Definition of Device (Legal)

- There is NO specific definition for a “device” in the DCA.
- DCA defines a “drug” as including any medicine or substance which is used for treatment, prevention, mitigation, diagnosis of disease or condition, and any devices notified as drugs by the Government.

Definition of Device (GCP)

- Indian GCP describes a device as "*an inert diagnostic or therapeutic article that does not achieve any of its principal intended purposes through chemical action, within or on the body unlike the medicated devices which contain pharmacologically active substances which are treated as drugs…*"

Definition of Drug

- "Drug" is an inclusive definition as per the Drugs & Cosmetics Act (DCA).

Note: all laws, rules, forms, correspondence are in British English

Unclear Regulation of Devices

- Devices are not properly defined; all regulation is of “drugs.”
- Different regulations applicable to different items.
- Procedures are not uniformly specified.
- No single list of devices or categorization of devices into classes exists.

India Drug/ Device Regulators (1)

- **Drug Controller General India (DCGI):**
  - DCGI is the key official in the Central Drug Standards Control Organization (CDSCO).
  - CDSCO is headquartered in New Delhi and has 4 zonal offices – meant to help local governments.
  - **Functions of DCGI/CDSCO:**
  - Approval of manufacturing certain drugs (vaccines, large volume parenterals, blood products, r-DNA derived), specific devices and new drugs.

India Drug/Device Regulators (2)

- **Drug Controllers of the State Food and Drug Administration:**
  - There are 35 officials and departments – one in each state, under the respective State Governments (Drug testing laboratories in each State).
  - **Functions:**
  - Issues licenses to manufacture pharmaceuticals and specified devices (with prior approval of DCGI for specified products).

India Drug Policy/ Price Regulators

- Department of Chemicals & Petrochemicals, under the Ministry of Chemicals & Fertilizers
- National Pharmaceutical Pricing Authority (under the above Ministry)

Proposed Structure for Drug/Device Regulation

- Create a **Central Drugs Authority of India** "CDA" (similar to the US FDA), with the Drug Controller of India (DCI) as CEO, in place of the CDSCO–with a regulatory mechanism and responsible for all manufacturing, import, export, registration, approval, quality / QA, certification, clinical trials, post-marketing surveillance.
- Define Medical Devices specifically under the DCA and provide rules and guidelines for their regulation.
- Legislation to create CDAI, definition of medical devices is pending in the Parliament (Drugs & Cosmetics Amendment Bill 2007or DCAB).
- New standalone legislation covering drugs and therapeutics for price control instead of using the DPCO (no such legislation proposed so far).

Proposed Device Regulation (1)

- At the same time under the Ministry of Science and Technology there is a proposed legislation (not yet placed before Parliament) called The Medical Devices Regulation Bill 2006 (MDRB) which has been drafted and posted for public comment.
- It envisages the creation of a **Medical Device Regulatory Authority of India** "MDRA" with a CEO – and a regulatory mechanism responsible for all manufacturing, import, export, registration, approval, quality / QA, certification, post-marketing surveillance of medical devices.
- All manufacturing and import licensing with MDRA.

Proposed Device Regulation (2)

- DCAB has a more elaborate definition of devices, but still classified as drugs as before
- MDRB definition of devices is broadly similar to the DCAB
- It is hoped that devices will be under the ambit of only one regulator at the same time

Devices Regulated in India (1)

- Disposable hypodermic syringes
- Disposable hypodermic needles
- Disposable perfusion sets
- Copper T IUD

Devices Regulated in India (2)

- “Critical” in-vitro diagnostic kits for HIV, HbsAg, HCV and blood grouping sera
- Other “non-critical” in-vitro diagnostic kits
- Sterilized sutures and ligatures
- Sterilized umbilical polyester/tape
- Surgical dressings (cloth)
- Clinical thermometers (not under DCA)
- Diagnostic X- Ray and radiation- based equipment (not under DCA)

Devices Regulated in India (3)

- Since March 1, 2006 the following items have been declared as drugs for regulation of import, manufacture and sale:
  - **Cardiac stents**
  - **Drug eluting stents**
  - **Catheters**
  - **Intra-ocular lenses**
  - **IV cannulae**
  - **Bone cement**
  - **Heart valves**
  - **Scalp vein sets**
  - **Orthopaedic implants**
  - **Internal prosthetic replacements (includes cardiac patches and occluders)**

Note: devices imported as non-sterile and sterilized thereafter are also covered as well as . All peripheral stents are regulated.

Devices Regulated in India (4)

- On March 20, 2009, CDSCO clarified that the following Sterile Medical Devices would also be covered : Spinal Needles
  - Insulin Syringes
  - Three Way Stop Cock as an accessory of I.V.Cannula/Catheter/Perfusion Set
  - Endotracheal tubes
  - Introducer Sheath
  - Annuloplasty Ring
  - Cardiac Patch
  - Cochlear Implant
  - Extension Tube
  - Close Wound Drainage Set

Contd…..

Devices Regulated in India (5)

Contd….

- Tracheotomy Tube with / without Cuff
- AV Fistula Needle
- Extension Line as a accessory of Infusion Set
- ANGO kit/PTCA/Cath Lab Kit
- Heart Lung Pack
- Measure Volume Set
- Flow Regulator as a accessory of Infusion Set
- Hemodialysis Tubing Set / Blood Tubing Set/Arterial Venous Tubing Set
- Dialysis Catheter

Agent/Importer

- If you do NOT have your own subsidiary, branch office or joint venture, it is critical to appoint a local agent and/or importer.
- Who can be an agent? Importer or another person.
- Agent represents the manufacturer for business in India.
- Importer is the holder of the import license and must have license to stock and sell drugs, as well as a license to manufacture if there is any re-processing or pre-packing involved.
- Agent and importer can be the same, or separate, if importer is not to have access to confidential material.
- The agent and/or importer is responsible for the manufacturer's business in India.

Import: Registration (1)

- All imported regulated devices must be registered by the manufacturer; i.e. registration of both the product and each facility that produces the product.
- "Manufacturer" is a company, unit or facility that manufactures drugs in a facility outside India, such facility being approved by the national regulatory authority of the country concerned, and with approval by the regulatory authority for free sale of the item within and/or outside the country.
- Manufacturer must either have a license to manufacture or sell drugs in India **OR** have an agent or importer who has a license.
- Agent or importer must be a legal entity in India.
- Application for registration must be submitted by agent/importer duly authorized to do so by power of attorney.

Import: Registration (2)

- Registration certificate requires application along with US $1,500 per facility and US $1,000 per product from that facility.
- Registration is a pre-requisite for obtaining an import license for all drugs, except in the case of non-critical IVD products.

Import: Registration (3)

- Form 40 submitted by the ***agent or importer***, must be accompanied by the power of attorney executed abroad, notarized in the country concerned.
- Schedule DI information requirements (with notarized copies of major documents—confidential material may be given on disk) include:
  - Particulars of manufacturer and premises
  - Particulars of drugs to be registered

Import: Registration (4)

- Undertakings:
  - Compliance with terms of registration certificate
  - To report any changes of manufacturing premises
  - Compliance with labeling and packing rules as per DCA

Import: Registration (5)

- To report administrative action taken in response to adverse reaction (market withdrawal regulatory restriction, cancellation of authorization, “not-of-standard quality report”) anywhere in the world and to stop marketing in India pending consultation with DCGI
- Compliance with further rules and regulations of the Government of India

Import: Registration (6)

- Schedule D II requirements (some overlap with D I—confidential material may be given on disk):
  - General: name of drug, description and therapeutic class, regulatory status; free sale certificate/certificate of pharmaceutical product; Drug Master File (notarized); GMP certificate in WHO format or CPP, etc.
  - Chemical and pharmaceutical information: chemical name, code number, generic name, structure, physicochemical properties, dosage form and its composition, specifications of active ingredients, test for identification, flow chart of manufacturing process, detailed test protocol, etc.

Import - Registration (7)

- Biological and bio-pharmaceutical information
- Pharmacological and toxicological information*
- Clinical Documentation*: In case of a new drug, a brief summary of clinical documentation along with approval letter of DCGI.

* Note: Pharmacological and toxicological information and clinical documentation is not required if the drug appears in the Indian Pharmacopoeia or if it appears in the US, European or British Pharmacopoeia and it is already approved for the applicant by the DCGI.

Import: Registration (8)

- Labeling and Packaging information: Labels as per the DCA (package insert should be in English), therapeutic indications include method of administration, contra-indications, special warnings for use, pregnancy and lactation if contra-indicated, side effects, antidote for overdosing, pharmaceutical information including list of excipients, shelf life as packaged for sale, after dilution or reconstitution, after first opening the container, precautions for storage, instructions for use.
- Special information for blood products, diagnostic kits and vaccines.

Registration of Devices Announced March 2006 (1)

- Form 40, Schedule DI and DII modified for devices but containing information under the following headings (details are specified in the instructions):
  - Applicant information: name, address, local agent, importer, Indian manufacturer
  - Copy of the plant master file: including the location and layout of premises, brief flowchart, details of manufacturing process, in-process quality control system, other activities at plant, system of conformity assessment followed, etc.

Registration of Devices Announced March 2006 (2)

- Product information: proprietary/brand name, description, intended use and method of use, contraindications, category, manual, label*, etc.
- Regulatory status: proof of approval from US FDA, CE certificate, Australia/Canada/Japan, ISO/EN certification of the manufacturing facility, countries where product is sold, countries where product has been withdrawn and reasons for withdrawal. Free sale certificate from the country of origin is essential.
- Master file (details of GMP employed): component/material used, device master file, functional test protocol, risk assessment as per ISO 14971, sterilization process and validation/verification, stability data or statement of established stability of material used, shelf life of the device, biocompatibility and toxicological data, device GMP certificate.

* Labels as per GHTF guidelines or ISO specifications would normally be accepted for import, however if there is variation from the essential requirements of the DCA it would be examined on merits

Registration of Devices Announced March 2006 (3)

- For devices containing medicinal product: data on safety, quality and utility of the medicinal substance, data on device compatibility with medicinal products, clinical data and research articles, batch release certificate for devices containing biological products of animal and human origin;
- For devices not approved in country of origin, reports of clinical trials, sales, certificates of satisfactory use from medical specialists, details of product complaints.
- Post-market surveillance: outline of the system in place/proposed to trace the device in case of complaint of functioning or non-conformance to standards and procedures followed/proposed to assess reported complaints.

Registration of Critical IVD kits

- Submission of Form 40, Schedule DI and DII.
- In addition, product dossier should include:
  - Details of source antigen/antibody, process control coating on base material such as nitrocellulose paper, strips, cards, ELISA wells.
  - Test protocol of the kits showing specifications and method of testing.
  - Detailed evaluation report of the National Control Authority of the country of origin, specimen batch test report for at least three consecutive batches with specifications of each testing parameter, detailed test.

Registration Process (1)

- For registration of new drug, prior approval from the DCGI is required before Registration can be applied for.
- After receipt of application with fees, evaluation begins.
- Drugs are tested in Central Laboratory.
- DCGI may require clinical testing in India or abroad.
- DCGI may visit the manufacturing premises during the process.
- No time line is specified for grant of registration, it could take up to a year.

Registration Process (2)

- Registration certificate in Form 41 is issued to the manufacturer.
- The registration certificate is valid for 3 years from the date of issue.
- Application for the renewal of registration certificate must be submitted no earlier than 9 months from certificate expiration date.

Registration Process (3)

- The importer can then apply for an import license from the DCGI.
- Importer submits Form 8/8A along with Form 9 signed by the manufacturer/ agent.
- The import license in Form 10/10A is valid for 3 years from the date of issue.
- Application for the renewal import license must be submitted no earlier than 3 months from the license expiration date.

Expediting Import Registration (1)

- Selection of agent/importer is very important.
- Professional regulatory advice should also be taken.
- Preferably no correspondence between manufacturer and DCGI before submitting formal applications; clarifications at this stage should be verbal.

Expediting Import Registration (2)

- **Before applying, obtain advice on whether the item is a drug or a "new" drug. It is preferable to avoid the new drug classification.**
- **For new products**
- **For fast tracking**
- When **committees** are set up for specific product groups, it may be beneficial to make a presentation to the committee.

Good Manufacturing Practices (1)

- Good Manufacturing Practices are provided in Schedule M of the DCA, which lists requirements for the factory premises, materials, plant and equipment.
- General requirements cover premises and materials including:
  - Location and surroundings (buildings, water systems, waste disposal), warehousing area, production area, ancillary area, quality control area
  - Personnel, health, clothing and sanitation, manufacturing operations and controls, sanitation in manufacturing premises
  - Control on raw material and equipment
  - Documentation and records, labels and printed materials

Good Manufacturing Practices (2)

- Specific additional requirements for:
  - Sterile products, small volume injectibles, large volume parenterals, and sterile ophthalmic preparations
  - Tables and capsules
  - Syrups, elixirs, emulsions and suspensions

Good Manufacturing Practices (3)

- Requirements of plant and equipment are provided for:
  - Creams, ointments, pastes, emulsions, lotions, solutions, dusting powders and similar products
  - Syrups, elixirs, emulsions and suspensions
  - Tablets
  - Powders
  - Capsules
  - Surgical dressing
  - Ophthalmic preparations
  - Pessaries and suppositories
  - Repacking of drugs and pharmaceutical chemicals
  - Small volume injectibles and large volume parenterals

Quality Assurance/Control (1)

- Schedule M describes the quality assurance, self-inspection and/or quality audit, and quality control systems requirements.
- Quality assurance systems should ensure:
  - Compliance with GMP, GLP, GCP
- Self-inspection and Quality audit:
  - Evaluation of compliance with GMP through a team of in-house and/or external experts to audit the implantation and results documented, including evaluation, conclusions, recommendations and follow-up actions, written instructions for self-inspection covering buildings, equipment, personnel, production quality control, documentation, hygiene, recall procedures, and label control

Quality Assurance/Control (2)

- Quality Control System: coverage should include sampling, specifications, testing, documentation, release procedures, not confined to laboratory operations alone. Issues to be covered:
  - Establishment of QC lab with staff, QC lab demarcated for chemical, instrumentation, microbiological and biological testing.
  - Storage area for reference samples, SOPs for sampling, inspecting and testing of all raw and in process materials, finished products and packaging materials.
  - Authorized and dated specifications for all materials, products, reagents, solvents, water.

Manufacturing License (1)

- All drug manufacturing requires a license under the DCA.
- Industrial license from the Central Government for specific products is no longer required.
- License can be only given to an entity based in India (partnership, foreign/ locally owned company, joint venture, subsidiary).
- State Government Drug Controllers can license most products.

Manufacturing License (2)

- License is given after application and inspection for compliance by the authorities.
- License is given for each factory and for the drugs made therein—there are different licenses depending on the product group. License is also given for third party premises (“loan licensing”).
- Applicant must comply with the requirements of Schedule M (Good Manufacturing Practice).

Manufacturing License (3)

- Conditions for grant/renewal of license include:
  - Compliance with Schedule M/ M III
  - Supervision by a full-time competent technical staff member with a degree in pharmacy/pharmaceutical chemistry/science from India or overseas and with experience in pharmaceutical manufacturing
  - Requirements of the testing laboratory and qualifications of the head of the testing unit

Manufacturing Medical Devices (1)

- Schedule M requirements may be relaxed by the licensing authorities for categories of drugs for which Schedule M does not explicitly provide yet.
- However, there are also general factory requirements for medical devices in Schedule M III.
- Schedule M III is much less detailed than Schedule M, and there is some overlap as regards to general requirements. However, there are specific process and equipment requirements for: sterile disposable perfusion and blood collection sets, sterile disposable hypodermic syringes and needles.

Manufacturing Medical Devices (2)

- In the case of critical IVD kits, the procedure is as below:
  - Application for license is made with product dossier and details of manufacturing facility.
  - Test manufacturing license is issued.
  - Product is evaluated by the National Institute of Biologicals.
  - Joint inspection by DCGI/State FDA for GMP compliance – Schedule M/M III.
  - License is issued.

Manufacturing Medical Devices (3)

- **In the case of devices notified on March 1, 2006, the procedure is as below**:
  - Application for license is made to the State FDA with a copy to the DCGI
  - Products not manufactured in the country before notification will need prior approval of the DCGI. Application should be accompanied with various details.
- **Manufacturing details:**
  - Details of company and manufacturing premises, copy of Site Master File
  - Brief highlights of the project, plans, devices to be manufactured
  - Manufacturing process, etc.
- **Product details**:
  - Brand name, description/category, intended use and method of use, medical specialty
  - Qualitative and quantitative particulars of constituents, specifications of materials used, etc.

Manufacturing Medical Devices (4)

- List of accessories and other devices to be used in combination, information on stability, details of clinical trials carried out if any, variations in shape, style, size, labeling details, physician's manual and promotional literature, packaging description and pack sizes, recommended storage conditions, summary indications of reported problems.

- For medical devices that are new or do not have any benchmark certification, expert committees will be set up to examine the information provided.

General Approvals for Manufacturing

- Besides a drug manufacturing license, there are other licenses/approvals required for manufacture. These are mainly at the State/local level. The major ones are:
  - License for capital goods import (rarely required)
  - License for raw materials import, rarely required (other than bulk drugs for which DCGI gives a license)
  - Land purchase/lease registration and building permission
  - Factories Act registration, registration with State Director of Industries

Labeling and Packing (1)

- As of now, labeling is in English, although there is a proposal to have dual language labels.
- No drug can be sold in India without appropriate labeling.
- Label must be in indelible ink
- Where required, the date of expiration of potency should be mentioned, and the period between date of manufacture and expiration should not exceed the specified period.
- Label must show the maximum retail price of the product inclusive of all taxes.

Labeling and Packing (2)

- If a drug has to be used under medical supervision, that must be mentioned; similarly, if it is for external use only, that should also be mentioned.
- Pack sizes have been recommended for certain drugs.
- The label should not contain any claims that the drug will cure certain specified diseases.
- In addition, under the Standard of Weights and Measures Act (SWM), all imported packages must bear the name and address of the importer.

Labeling and Packing (3)

- In addition, there are specific labeling requirements for the following devices:
  - Non-sterile surgical ligature and suture
  - Cloth bandages
  - Condoms
- For imported devices, labeling as per GHTF guidelines or ISO specifications would usually be accepted, however if there is variation from the essential requirements per the DCA, it would be examined on merits

Price Control

- Drug prices in India are among the lowest in the world – this is due to low costs, to absence of product patents till 2005 but mainly due to price control.
- Certain bulk drugs and their formulations are under price control since 1970, by virtue of the Drug Price Control Order (the latest order being in 1995). However definition of drug under this order is not the same as under the DCA and hence excludes devices.
- 74 drugs covering 40% of retail sales, are in the price control list ("scheduled bulk drugs and formulations"). The list has progressively been brought down from 347 in 1970.

Intellectual Property Rights (1)

- India has had a Patent Law since 1856.
- The modern law is the Patents Act 1970 as amended from time to time.
- Until 2005, devices could be patented but drugs were not covered as products; only the manufacturing processes were covered.
- After changes to the Patents Act in 2005, drugs may also be patented.
- Foreign companies have got their drugs patented in India under the new legislation.

Intellectual Property Rights (2)

- Variations of existing products such as salts, esters, pure forms, etc may not be patented unless there is proof of innovation.
- Patent applications may be challenged within India and three month's time is given for notice of opposition.
- Patents if granted are for 20 years from the date of filing the application (for filings before January 1, 2005 under the previous law 20 years from the date of grant of patent).
- However, there is as yet no legislation for data protection.

Thank you for your consideration!

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