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REGULATORY REQUIREMENTS FOR CANCER IMMUNOTHERAPY PRODUCT DEVELOPMENT : INDIAN PERSPECTIVE

Disclaimer

The views expressed in this presentation are my own, and I have no conflict of interest to disclose.

Cancer Burden in India

- ~ 1 Million new diagnosed cases every year
- 600000-700000 deaths per year
- Mostly related to tobacco use, infections related
- Social factors, inequalities are the reasons for the burden

www.thelancet.com/oncology Vol 15 May 2014

Cancer incidence and mortality in India regions, 2012

	Incident cases	Deaths	Incidence ASR	Mortality ASR	Mortality to Incidence ratio
Very high HDI	5 780 821	2 606 104	279·2	105·3	37·7
High HDI	2 126 439	1 244 496	180·2	102·3	56·8
Medium HDI	5 232 474	3 656 562	144·2	102·8	70·9
Low HDI	943 102	690 141	112·8	86·7	76·9
India	1 014 934	682 830	94·0	64·5	68·6

HDI=human development index. Data from GLOBOCAN online analysis for 2012.1 ASR=age-standardised rate, adjusted for world population and in 100 000 population.

Modalities of treatment:

1. **Local therapy:**
   - **Surgery.**
   - **Radiation therapy.**
2. **Systemic treatment:**
   - **chemotherapy.**
   - **Hormonal therapy.**
   - **Radioactive material.**
3. **IMMUNOTHERAPY.**

Types of cancer immunotherapy

The main types of immunotherapy now being used to treat cancer include:

- **Monoclonal antibodies:** designed to attack a very specific part of a cancer cell.

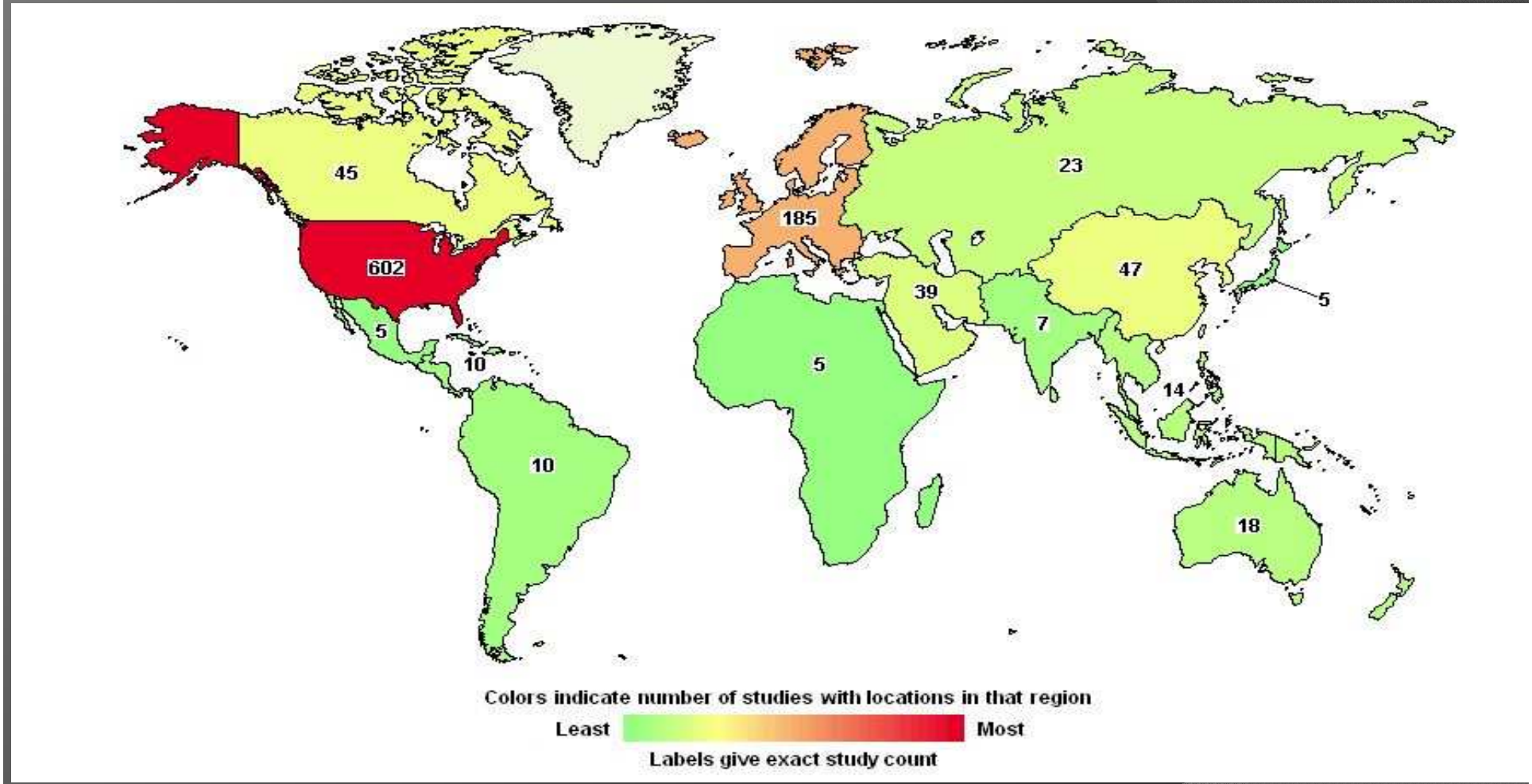
- **Immune checkpoint inhibitors:** to 'brakes' off the immune system, which helps it recognize and attack cancer cells.

- **Cancer vaccines:** Vaccines are substances put into the body to start an immune response against certain diseases. We usually think of them as being given to healthy people to help prevent infections. But some vaccines can help prevent or treat cancer.

Future Of Immunotherapy

- Clinical research in immunotherapy is rapidly increasing:
- From 2009 to 2012, abstracts at major conferences have doubled.
- There are approximately 800 ongoing clinical trials in various phases for cancers such as breast, colon, head and neck, and kidney.

Immunotherapy *AND* Cancer: Clinical Trials*



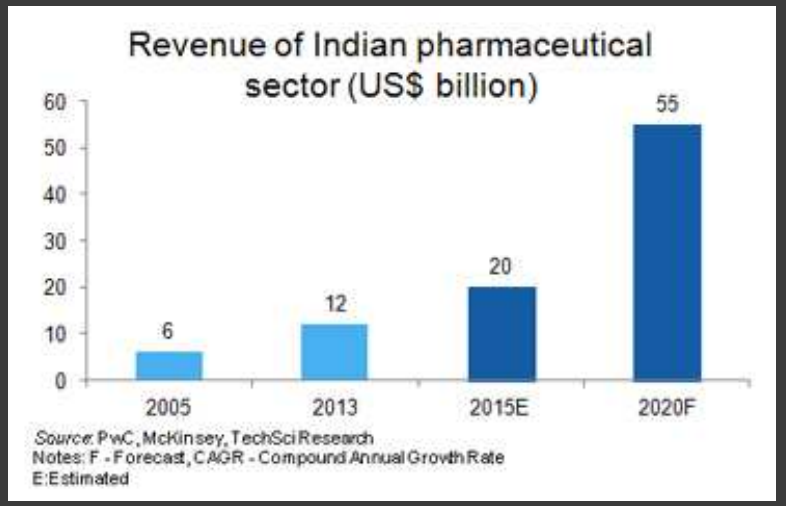
* source: Clinical trial registry of US, available at www.clinicaltrials.gov, accessed on 27/July/2013

Critical Hurdles in Cancer Immunotherapy Identified

- Limitations of current animal models to predict efficacy of cancer immunotherapy strategies in humans
- Prolonged time to obtain approval to initiate clinical trials
- Complexity of cancer, tumor heterogeneity and immune escape
- Limited availability of reagents for combination immunotherapy studies
- Limited funds available to translate science into patients
- Lack of definitive biomarker(s) for assessment of clinical efficacy of cancer immunotherapies
- Conventional clinical response criteria do not take into consideration differences between response patterns to cytotoxic agents and immunotherapies
- Paucity of teams of scientists and clinicians dedicated to translational research in cancer immunotherapy
- Insufficient exchange of information critical to advancing the field

Trends in Indian Pharma sector revenue

- The Indian pharmaceuticals market increased at a CAGR of 12.79 per cent in 2015 from US$ 6 billion in 2005, and is expected to expand at a CAGR of 15.92 per cent to US$ 55 billion by 2020
- By 2020, India is likely to be among the top three pharmaceutical markets by incremental growth and sixth largest market globally in absolute size
- India's cost of production is significantly lower than that of the US and almost half of that of Europe. It gives a competitive edge to India over others.



Indian Biopharma Market

- Pharmaceutical and health biotechnology is India's one of the fast growing sector
- Bioparmaceuticals account for 64% of the India's biotech industry
- Value for >4Bn USD
- Growing 20-25% per annum
- Consists of vaccines, bio-similar, constitute the largest component of the Indian bio-pharma segment

Characteristics of Indian Bio-pharma Market

- Growth in India is primarily export driven
  - Export sales are rising at rate of 47%
  - Domestic sales have risen only up to 6% per year
- Vaccines are the largest and fastest growing sector
  - Currently account for about 43% of India's total biopharmaceutical sales
- Industry growth is concentrated in a small number of companies
  - ~30 companies account for majority of sales
  - Led by Biocon, Serum Institute, Zydus, Panacea Biotech….
  - And India-based subsidiaries of MNCs

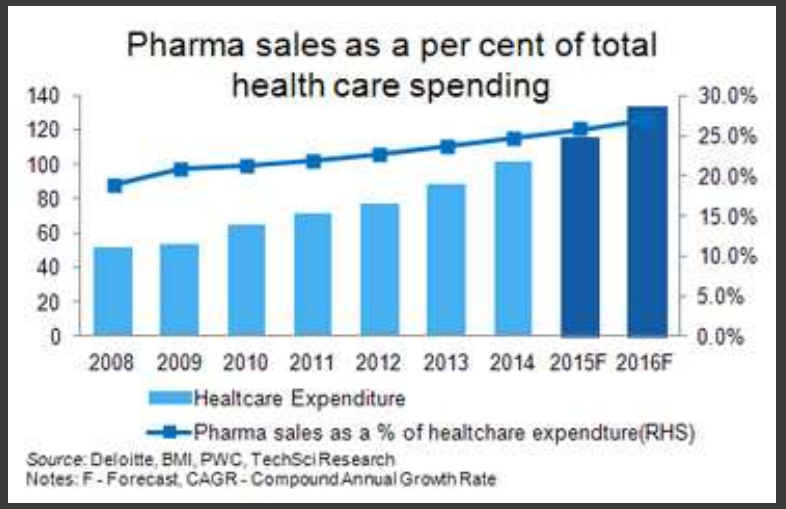
Characteristics of Indian Biopharma Market

- Indian companies manufacture wide range of biopharmaceuticals
  - Include recombinant insulin, EPO, G-CSF, recombinant hepatitis-B vaccine, streptokinase, interferon alpha-2b, rituximab, and anti-EGFR & anti-VEGF Mab products
- Indian bio-pharamceuticals R & D is increasing rapidly
- since 2003, the R & D budgets of the top 10 Indian pharma companies have more than doubled

Steep growth expected in pharmaceutical expenditure

Latest update: September, 2015

- Over 2012–20, total healthcare spending is expected to rise at a CAGR of 20 per cent to US$ 280 billion from US$ 65 billion
- Industry revenues are expected to expand at a CAGR of 12.1 per cent during 2012-20 and reach US$ 45 billion
- Pharmaceutical sales, as a percentage of total healthcare spending, are expected to increase to 27 per cent by 2016 from 18.9 per cent in 2008nbsp;



Strength India

- Health/pharmaceutical biotechnology is one of India's fastest growing sectors
- India has innovative as well as bio-similar biotech capabilities
- Indian biotech companies are growing at ~20-25% rate per annum
- Biologics patent cliff offers Indian companies a huge opportunity
- Capability-benchmarking is the key for any company planning to generate value from the biologics patent cliff
- Entering bio-similars market is facilitated by acquiring or developing R&D, manufacturing, supporting activities, marketing or lobbying
- India has >70 active CROs engaged in BE & Clinical trials which are cost effective, professional,
- IPR-sensitive and offer high quality services Steep competition among CROs, quality of data, financing, and excellence in human resources are major challenges

Regulatory Scenario

Regulatory Requirements for Marketing Authorization of Biological Products

- **Drugs and Cosmetics Act & Rules, 1945.**
- **Guidance for Industry**
  - ✓ **Specific for Biological Products**
- **Indian Pharmacopoeia Standards**
- **SOPs and Various Checklist**

GOVERNMENT OF INDIA

MINISTRY OF HEALTH AND FAMILY WELFARE

(Department of Health)

THE DRUGS AND COSMETICS ACT AND RULES

THE DRUGS AND COSMETICS ACT, 1940

(23 OF 1940)

(As amended up to the 30th June, 2005)

and

Drug & Cosmetic Act 1940

Act to regulate the import, export, manufacture, distribution and sale of

- drugs
- Cosmetics

To ensure their safety, efficacy, quality and conduct of clinical trials and for matters connected therewith or incidental thereto.

Drug, Cosmetics and Medical Devices Act, 16th August 2013

Drug & Cosmetics Act

Amendment August 2013

- Drugs, Investigational New Drugs, Medical Devises, Investigational New Devices and Cosmetics
- Biologicals – Third Schedule, Section 18(3)
- Registration of Institutional Ethics Committees
- Central Drug Authority
- Technical Advisory Committees for new categories
- Cell Biology Based Therapeutic Drug Evaluation Committee (CBBTDEC)

“THE THIRD SCHEDULE [Section 18(3)]

- Sera;
- Solution of serum proteins intended for injection;
- Vaccines; and includes DNA vaccines and vaccines containing living genetically engineered organisms;
- Toxins;
- Antigens and anti-toxins;
- Anti-biotics (betalactums and cephalosporins);
- Parenteral preparations meant for parenteral administration;
- Hormones and preparations containing hormones;
- r-DNA derived drugs;
- RNA interference based products;
- Monoclonal anti-bodies;
- Cellular products and stem cells;
- Gene therapeutic products;
- Xenografts;
- Cytotoxic substances (anti-Cancer drugs);
- Blood products;
- Modified Living Organism

Guidance for Regulatory Approvals for SCCP, 2014

AIM :

- To define the role of CDSCO in regulating the manufacturing, licensing and usage of SCCPs
- To describe the various categories of licensing / approvals for facilities, clinical trials and protocols for SCCP usage for specific indications.
- To provide guidance to the applicants for isolation, characterization, culturing, processing, manufacturing, quality control, labeling and distribution of SCCPs.
- To provide guidance for compliance, with all the regulatory requirements, to carry out clinical trials with SCCPs

Scope

Rules and regulations in this Guidance Document shall apply to all organizations that wish to use SCCPs for therapeutic purposes in India. The organizations include:

- ✓Hospitals
- ✓Private clinics
- ✓Institutes
- ✓Universities,
- ✓Tissue banks and
- ✓Companies

Regulatory approval for SCCPs

- All stem cells and cell based products that can be used for therapeutic purposes shall be referred as Stem Cell and Cell Based Products (SCCPs) and all activities related to their usage i.e. manufacture/isolation/ collection, storage and transplantation into patients must be done only under a license or permission that would be granted by the DCG(I)/CDSCO.

- All products and applications, other than bone marrow transplantation/blood transfusion for replacement therapy, shall be considered as SCCPs and hence it should be done under a license.

Categories of Licenses/approvals

- Category 1: License for collection, processing , storage of SCCP for the purpose of test and analysis
- Category 2: Approval of Clinical Trial Protocol s for generation of safety and efficacy data
- Category 3: Approval/permission for manufac ture or import of SCCP as a IND/New Drug
- Category 4: License for manufacture or impor t for storage, sale and distribution

Procedure for Application for Marketing Authorization (Cont.)

- **Form 44: As per Drugs and Cosmetics Act, 1940 and Rules 1945 made there under Form 44 is the application for grant of permission to import or manufacture a New Drug or to undertake clinical trial. The necessary information to be submitted as a part of Form 44 includes following:**

1. Particulars of New Drug

(1) Name of the drug

(2) Dosage Form

(3) Composition of the formulation

(4) Test specification

(i) active ingredients

(ii)inactive ingredients

(5) Pharmacological classification of the drug

(6) Indications for which proposed to be used

(7) Manufacturer of the raw material (bulk drug substances)

(8) Patent status of the drug.

Procedure for Application for Marketing Authorization

- ✓ **Firm intending to market a new drug has to apply to CDSCO (HQ) with the documents as per the prescribed checklist**

http://www.cdsco.nic.in/writereaddata/2014check_ma_nda.pdf

- ✓ **The application for grant of New Drug Permission has to be in Form 44**

- ✓ **The fees to be accompanied with Form 44 is Rs 50000/-. Any subsequent change/ approval shall accompany with the fee of Rs 15000/-.**

- ✓ **Firm needs to submit the application along with CTD dossier in respect of the product**

Procedure for Application for Marketing Authorization (Cont.)

Data submitted along with the application

A. Permission to market a new drug :-

(1) Chemical and Pharmaceutical information

(2) Animal Pharmacology

(3) Animal Toxicology

(4) Human / Clinical Pharmacology (Phase I)

(5) Exploratory Clinical Trials (Phase II)

(6) Confirmatory Clinical Trials (Phase III) (including published review articles)

(7) Bio-availability, dissolution and stability study Data

(8) Regulatory status in other countries

(9) Marketing information

(a) Proposed product monograph

(b) Drafts of labels and cartons

(10) Application for test license

Procedure for Application for Marketing Authorization (Cont.)

B. Subsequent approval / permission for manufacture of already approved new drug :

(a) Formulation:

(1) Bio-availability / bio-equivalence protocol

(2) Name of the investigator/center

(3) Source of raw material (bulk drug substances) and stability study data.

(b) Raw material (bulk drug substances)

(1) Manufacturing method

(2) Quality control parameters and/or analytical specification, stability report.

(3) Animal toxicity data.

C. Approval / Permission for fixed dose combination:

(1) Therapeutic Justification (authentic literature in pre-reviewed journals/text books)

(2) Data on pharmacokinetics / pharmacodynamics combination

(3) Any other data generated by the applicant on the safety and efficacy of the combination.

Procedure for Application for Marketing Authorization (Cont.)

D. Subsequent Approval or approval for new indication – new dosage form

(1) **Number and date of Approval / permission already granted.**

(2) **Therapeutic justification for new claim / modified dosage form**

(3) **Data generated on safety, efficacy and quality parameters**

- **Completed applications in all respects after getting screened at prescreening counter shall be submitted to the office. Query if any shall be cleared on site or the additional document if required by the Screening Authority shall be submitted.**

As per the CDSCO Guidance for Industry - Requirements for permission of New Drug Approval, the application has to be submitted in Common Technical Document (CTD format) which is as per the International submission requirements and has five Modules:

- **Module I: Administrative/Legal Information**
- **Module II: Overall Summaries**
- **Module III: Quality Information (Chemical, Pharmaceutical and Biological)**
- **Module IV: Non-Clinical Information**
- **Module V: Clinical Information**

Module 3: Quality Information (Chemical, Pharmaceutical and Biological)

3.1	Table of contents for Module 3
3.2	Quality contents
3.2.S	Drug substance(s): Information must be submitted for each drug substance in the product.
3.2.S.1	General information, starting materials and raw materials
3.2.S.2	Manufacturing process for drug substance
3.2.S.3	Characterization of drug substance
3.2.S.4	Quality control of drug substance
3.2.S.5	Reference standards
3.2.S.6	Container closure system
3.2.S.7	Stability of drug substance

Module 3: Quality Information (Chemical, Pharmaceutical and Biological)

3.2.P	Drug product
3.2.P.1	Description and composition of drug product
3.2.P.2	Pharmaceutical development
3.2.P.3	Manufacture of drug product
3.2.P.4	Control of excipients (adjuvant, preservative, stabilizers and others)
3.2.P.5	Control of drug product
3.2.P.6	Reference standards of materials
3.2.P.7	Container closure system
3.2.P.8	Stability of drug product

Module 3: Quality Information (Chemical, Pharmaceutical and Biological)

3.2.A	Appendix
3.2.A.1	Details of equipment and facilities for production of drug product: master formula, batch record and set release documentation in respect of consistency batches
3.2.A.2	Safety evaluation of adventitious agents
3.3	Bibliographic Reference

Process of approval/ testing before the products are released in the market

- **As per Rule 122 E, 122A and 122B of Drugs and Cosmetics Rules, 1945, the products coming under the definition of New Drug shall require Marketing Authorization in Form 45 (for import and marketing) or Form 46 (for manufacture and marketing) in India.**
- **The firm intending to import/manufacture and market any Biological Product viz. vaccines, recombinant products, stem cells etc. has to apply in Form 44 to this Directorate for grant of Marketing Authorization.**
- **This may or may not require a clinical trial in Indian population.**

Process of approval/ testing before the products are released in the market

- **Clinical Trial application in Form 44 along with CTD module and other related documents is submitted to CDSCO for evaluation.**
- **After satisfactory review of the application the proposal may be referred to subject expert committee (SEC) for evaluation and subsequently to the technical committee for further deliberation.**
- **On receipt of recommendations from both the committees the clinical trial permission is granted to the firm. In case of New Chemical Entities (NCE), the proposal may be referred to IND committee followed by technical committee and apex committee for recommendation and further action.**

Process of approval/ testing before the said vaccines are released in the market

- **Waiver of Clinical Trial in Indian population for approval of new drugs, which have already been approved outside India, can be considered only in cases of national emergency, extreme urgency, epidemic and for orphan drugs for rare diseases and drugs indicated for conditions/diseases for which there is no therapy.**

- **Whether the proposal of the firm shall be considered for waiver of clinical trial is decided by three tier review process i.e. Sequential review by Subject Expert Committee, Technical Committee and Apex Committee.**

Process of approval/ testing before the products are released in the market

- **Presently, there are provisions under rule 122A (2) and rule 122B (3) for waiver of local clinical trial in public interest. Schedule Y further provides that requirements of clinical trial may be abbreviated, deferred or omitted for drugs indicated in life threatening / serious diseases or diseases of relevance to Indian Health scenario.**

- **After successful completion of trial, the firm submits the study report, which is then evaluated by CDSCO and further reviewed by the subject expert committee.**

Monoclonal Antibodies (MAbs) approved by DCG (I) in India

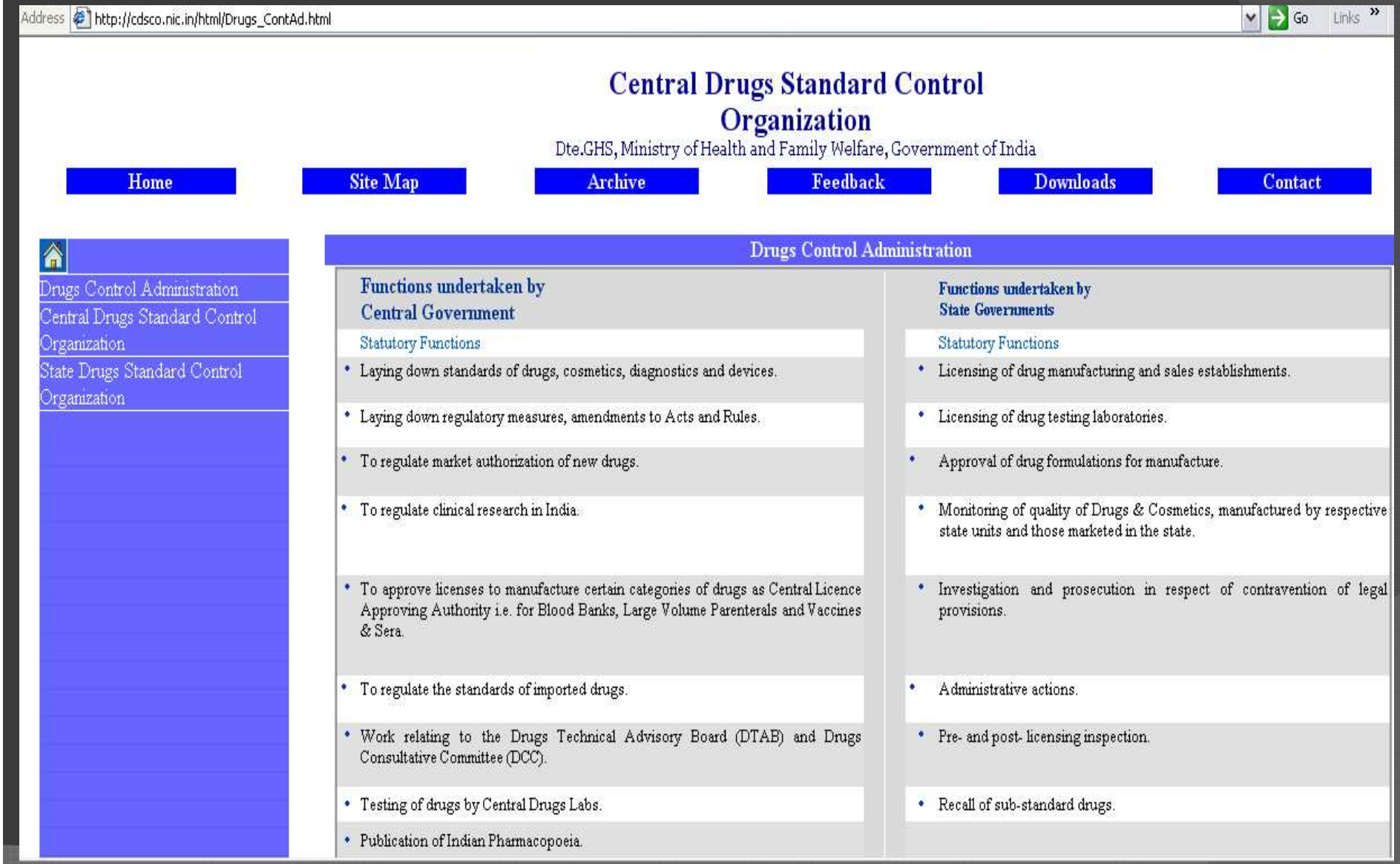
Name of the manufacturer	Name of Product	Year of Approval	Therapeutic Indications
Dr. Reddy's Laboratories ltd Zenotech Laboratories Intas Biopharmaceuticals Reliance Life Sciences M/s Hetero Ltd	Rituximab	22-03-2007 27-Feb-13 26-Feb-13 02-12-2015 25.03.2015	• relapsed or chemo resistant Indolent B cell Non-Hodgkin's Lymphoma • stage III-IV follicular lymphoma in combination with chemotherapy.
Biocon Ltd M/s Reliance Life Sciences	Trastuzumab	23-Oct-13 02-Jun-15	• adjuvant treatment of HER2 over expressing node =ve or node -ve (ER/PR –ve high risk breast cancer • Metastatic Gastric Cancer
Biocon Limited	NIMOTUZUMAB	30.08.2006	FOR THE TREATMENT OF HEAD AND NECK CANCER

Imported Monoclonal Antibodies (MAbs) approved by DCG(I) in India

Name of Firm (Importing)	Name of the Product	Year of Approval	Therapeutic Indications
M/s Roche (India) Scientific Ltd Mumbai M/s Emcure Pharmaceuticals Ltd M/s Taksal Ltd	Rituximab	08-10-2002 29/06/12 21/08/12	Treatment of patients with release or chemo resistant indolent B cell Lymphoma
M/s Wyeth Lederle Ltd	Gemtuzumab Ozogemicin (Lyophilized Powder)	12-09-2002	treatment of acute myeloid leukemia
M/s Roche Scientific Company M/s Emcure Pharmaceuticals Ltd Taksal pharma pvt. Ltd.	Trastuzumab	11-10-2002 29/06/12 26/07/12	In combination with an aromatase inhibitor for the treatment of patients with HER2-positive and hormone receptor-positive metastatic breast cancer.
Roche Scientific Company Emcure Pharmaceuticals Ltd	Bevacizumab Injection	17-01-2005 21/08/12	Treatment of colorectal cancer
GlaxosmithKline Pharmaceutical GSK	Denosumab (XGEVA)	3.10.12 17.10.2014	for the prevention of skeletal related events in patients with advanced malignancies involving bone
GSK	PANITUMUMAB (Vectibix)	19-Mar-13	EGFR expressing metastatic colorectal carcinoma with non-mutated (wild type) KRAS

Imported Monoclonal Antibodies (MAbs) approved by DCG(I) in India

Name of Firm (Importing)	Name of the Product	Year of Approval	Therapeutic Indications
GSK Limited	Ofatumumab (Arzerra) 20 mg/ml	01-Apr-14	Chronic lymphatic leukaemia (CLL)
M/s Roche Pvt. Ltd	Obinutuzumab inj	01-02-2015	in combination with Chlorambucil, is indicated for the treatment of patients with previously untreated chronic lymphocytic leukemia (CLL)
M/s Roche Pvt. Ltd	Pertuzumab	29/12/2014	in combination with trastuzumab and docetaxel for patientys with HER2-positive metastatic or locally recurrent unresectable breast cancer.
M/s Roche Pvt. Ltd	Trastuzumab emtansine	18/12/2014	is indicated for the treatment of patients with HER2-positive, unresectable locally advanced or metastatic breast cancer.
Biocon Biopharmaceuticals Biocon Biopharmaceuticals	NIMOTUZUMAB	28-Jun-06 27/Feb/13	For The Treatment Of Head And Neck Cancer


Address http://cdsco.nic.in/html/Drugs_ContAd.html
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Links
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Dte.GHS, Ministry of Health and Family Welfare, Government of India
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Drugs Control Administration
Central Drugs Standard Control Organization
State Drugs Standard Control Organization
Drugs Control Administration
Functions undertaken by Central Government
Statutory Functions
Laying down standards of drugs, cosmetics, diagnostics and devices.
Laying down regulatory measures, amendments to Acts and Rules.
To regulate market authorization of new drugs.
To regulate clinical research in India.
To approve licenses to manufacture certain categories of drugs as Central Licence Approving Authority i.e. for Blood Banks, Large Volume Parenterals and Vaccines & Sera.
To regulate the standards of imported drugs.
Work relating to the Drugs Technical Advisory Board (DTAB) and Drugs Consultative Committee (DCC).
Testing of drugs by Central Drugs Labs.
Publication of Indian Pharmacopoeia.
Functions undertaken by State Governments
Statutory Functions
Licensing of drug manufacturing and sales establishments.
Licensing of drug testing laboratories.
Approval of drug formulations for manufacture.
Monitoring of quality of Drugs & Cosmetics, manufactured by respective state units and those marketed in the state.
Investigation and prosecution in respect of contravention of legal provisions.
Administrative actions.
Pre- and post- licensing inspection.
Recall of sub-standard drugs.


Address http://www.ctri.in/Clinicaltrials/index.jsp
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Trial registration made mandatory by DCGI
As per DCGI decision, trial registration, before the enrollment of the first patient has become mandatory for all
The Clinical Trials Registry- India (CTRI) has been set up by the ICMR's National Institute of Medical Statistics (NIMS) and is funded by the Department of Science and Technology (DST) through the Indian Council of Medical Research (ICMR). It also receives financial and technical support through the WHO, WHO-SEARO, and the WHO India Country office. [Read more...]
Mission
The mission of the Clinical Trials Registry-India (CTRI) is to encourage all clinical trials conducted in India to be prospectively registered before the enrollment of the first participant and to disclose details of the 20 mandatory items of the WHO International Clinical Trials Registry Platform (ICTRP) dataset. [Read more...]
Vision
The vision of the CTRI is to ensure that every clinical trial conducted in the region is prospectively registered with full disclosure of the 20-item WHO ICTRP dataset, as well all items of the CTRI dataset, in order to 1) improve transparency and accountability, 2) improve the internal validity (details of the
WHO
ICMR
DST
Clinical Trials Registry-India (CTRI)
The CTRI is an online register of clinical trials being conducted in India. Any researcher who plans to conduct a trial involving human participants, of any intervention (drug, surgical procedure, preventive measures, lifestyle modifications, devices, educational or behavioral treatment, rehabilitation strategies and complementary therapies) are expected to register the trial in CTRI before enrollment of the first participant. Registration is voluntary but some fields marked* are mandatory for registration to proceed. Some fields marked WHO also need to be filled if the trial is to receive a registration number and fulfill WHO/ICMJE requirements. Incomplete entries will be given a provisional registration number that will not suffice for purposes of publication in journals that endorse the ICMJE recommendations for trial registration. Registration of trials in the CTRI is free. All registered trials will be made publicly available. The CTRI will be

THANK YOU…..