



Asian Harmonization Working Party

WORKING TOWARDS MEDICAL DEVICES HARMONIZATION IN ASIA

AHWP Member Economy – India Clinical Trial Regulatory Update

29thNov'2010 AHWP Meeting Riyadh

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Medical Device Regulations - India

Ad hoc Approach

1989 - 95

Devices Regulated

- Contraceptives
- Hypodermic Syringes
- Needles
- IVD for HIV
- Surgical sutures
- Medicated tapes and
- Surgical dressing.

2002-04

ICMR, DRDO and MoH involved in making proposals for MD regulation.

Expert Committee formed by MoH GOI

2005

Sub standard DES banned

Court directed DCG(I) to reg. devices

Drug Regulations for MD

2006

DCG(I) framed guidelines for import of MD.

Issued clarifications on guidelines

31st Dec. deadline for application submission.

2007

DCG(I) issued clarification on FSC, Reg. status and CTS requirement.

2008

DCG(I) drafted Sch. III (MD cGMP for mftr) guideline

2009

Clinical Trails mandated to be registered with ICMR

2010

Draft guidance issued for CSTD and Clinical Trail

Structured Approach

2010-11

Phase I implemented

For Class C and D devices that constitute around 20% market share.

High Risk Devices (Cardiac Stents etc)

2011-12

Phase II implemented

For Class B, C and D devices.

They constitute around 80% of the market.

2012-13

Phase III implementation

Classes i.e. A, B, C and D

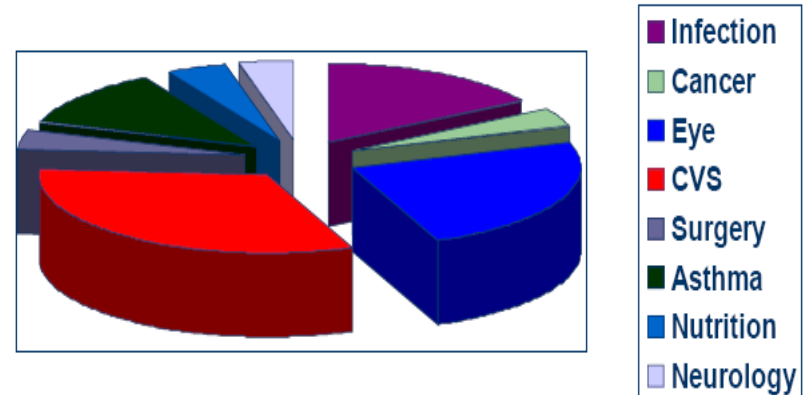
All the devices on market will be regulated



Clinical Trial Market- India

India - Hotspot

- Genetically diverse population
- Low cost 40 – 60% reduction.
- Large and quick patient recruitment.
- Over 600 ICH/GCP compatible sites.
- Large no. of medical specialists
- Well developed infrastructure.
- Increase in no. of CROs (National and International)



Source : ClinicalTrials.gov

Issues

- Truly Independent Investigational Review Boards.
- Under reporting by patients, physician etc.
- Change in follow ups.
- Change in study coordinators.
- Regulatory apparatus.



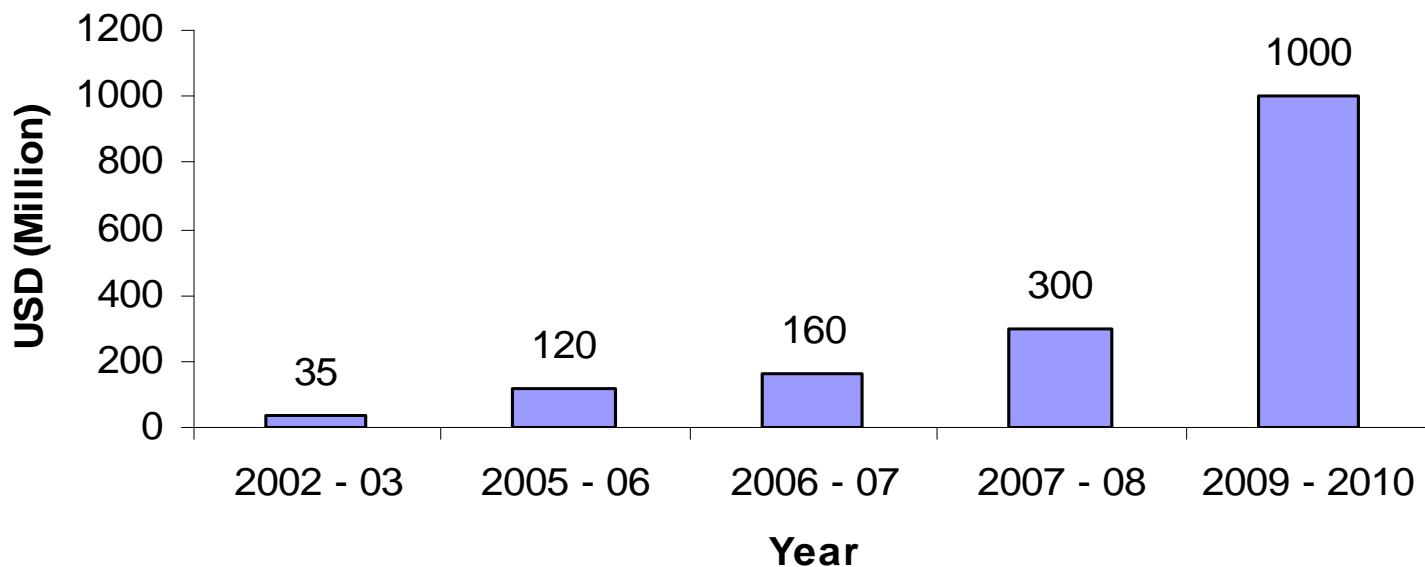
Growth of Indian Clinical Trial Industry

| | | | |
|------------------------------|-----------------------|---------------------|-------|
| Patient Pool | Scanty | Large | India |
| Patient Recruitment Rate | Lowest rate | Highest rate | India |
| Speed | Low | High | India |
| Cost | Most expensive | Least expensive | India |
| Facility & Investigator Pool | Smallest pool | Highest pool | India |
| Industry Trial Experience | Least experience | Most experience | India |
| Regulatory Environment | Least Conducive | Most Conducive | India |
| Quality of Data | Unacceptable to EU/US | Acceptable to EU/US | India |



Growth of Indian CT Industry

Growth of Indian Clinical Trial Industry



As per FICCI - Ernst & Young Survey Report 2008, India can attract between 5 - 10% of the global contract research outsourced market (all services including chemistry, toxicology and clinical research) over next 5 years.



Govt. Facilitating Fiscal Incentives for CT

- No import duty on CT (Clinical Trial) supplies (2003)
- Exemption from registration requirements for clinical trial Supplies (2003)
- Export of clinical trial related biological specimens allowed, based on protocol approval (2005)
- Exemption from Service Tax on new Drug testing (2007)

Governance & Control of C T

| Regulatory Bodies | Ministry | Roles |
|---|---|--|
| <p>DCGI (Drug Controller General of India)</p> <p>CDSCO (Central Drugs Standard Control Organization)</p> | <p>Ministry of Health and Family Welfare</p> | <ul style="list-style-type: none"> ➤ Permission and Approval for conducting Clinical Trails ➤ Granting Import license and Test License ➤ Permission /NOC/Notification of protocol amendments/ICF amendments/Safety reports. ➤ Notification for Serious Adverse Events observed in ongoing CTs. |
| <p>Directorate General of Foreign Trade</p> | <p>Ministry of Commerce & Industry</p> | <p>Export Permission for exporting Human Biological sample for study related analysis</p> |
| <p>Indian Council Of Medical Research (ICMR)</p> | <p>Apex body for the formulation, coordination & promotion of biomedical research.</p> | <p>Registration of Clinical trials in India, through CTRI (Clinical Trial Registry India)</p> |



CDSCO Goals for C T

2008 -09

- Training for Clinical Trials site inspections
- Robust review process for Clinical Trial proposals
- Registration of CROs
- Inspection of Clinical Trial sites in the country.
- Guidelines for Registration of Ethics Committees/IRBs
- Mandatory registration of Clinical Trials

2010 – 2015

- Ensuring penal provisions for fraud & misconduct in Clinical Research
- Registration of Clinical Trial sites and Ethics Committees/IRBs
- Creation of environment for Phase 0 and micro dosing studies.



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Current CT Regulatory Process

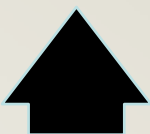
Mfr. Site
Master file

Quality & Compliance

ISO /POA

Schedule DI & DII - Signed undertaking by the Mfr for Mfr Site & Products

Rule 122-A



Data from
local trial

- Ph I/II Global data
- Ph III Local data
- Import permit for Clinical Supplies
- Permission for Clinical Trial

Rule 122-DA



Trial requires prior
permission

Rule 122-E



New device
• > 4 years
• Diff claims

Schedule Y- Guidance Clinical Trial Requirements



Clinical Trials Regulations

- The current status of clinical trials for medical devices is as per [Schedule Y, GCP and ICMR guidelines](#).
- Draft guidelines/regulations for clinical trials has been released on [4th Aug. 2010](#), but it has not yet been implemented as regulation.
- All trials being conducted in India should be registered to [Clinical Trial Registry India \(CTRI\)](#).



Clinical Trials Regulations (Contd.)

- Mandatory trials are required for new/innovative products where all the three phases, Phase II, Phase III and Phase IV are conducted to evaluate the safety and performance/efficacy of the product .
- In India Phase I is restricted i.e. not allowed for foreign innovative products.
- Pre Clinical and Phase I study data are required for the approval of the further phases to be conducted in India.



Registration Process of CT

- After obtaining the No Objection Certificate from DCGI
- Sponsors to register the Clinical Trial at ICMR's (Indian Council of Medical Research) web based Clinical Trial Registry site (www.ctri.in)



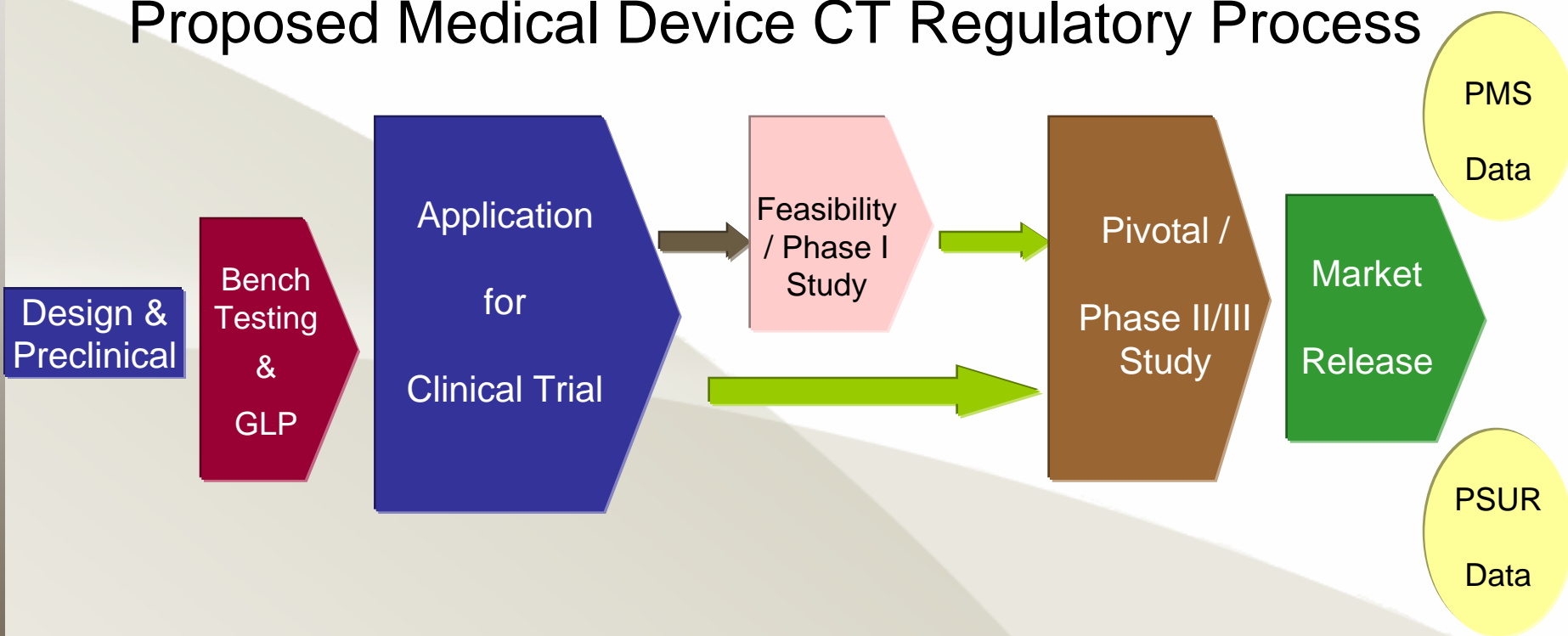
Registration Process of CT (contd.)

- Trial registration on [ClinicalTrial.gov](https://clinicaltrials.gov) is done through Protocol Registration System (PRS).
- National Clinical Trial (NCT) number is generated during the process of registration.
- It is an eight digit number.
- Form is available to fill the essential information related to trial.
- Finally considered registered on loading the completely filled form electronically.



Proposed CT Process

Proposed Medical Device CT Regulatory Process





Clinical Trials Documentation

01. Form 44
02. Fee
 - Rs 50,000 for Feasibility/Phase I study
 - Rs 25,000 for Pivotal/Phase II/III study
03. Protocol
04. Global Reg. Status of Device
05. Approvals
06. Forms
07. Investigators brochures
08. SUSAR
09. Affidavit
10. Clinical Study Report (if any)



Requirements Form 44

Devices Particulars

- Name and Address of the manufacturer.
- Generic Name
- Brand Name
- List of accessories to be used with the parent device

Technical Documents

- Labeling details
- Packaging descriptions
- Variations in shape and size of the devices
- Physician manual and promotional literature (English)
- Composition of Device
- Qualitative & Quantitative aspects of particulars
- Information on sterility & stability of the product

Administrative Documents

- Indication with respect to which clinical study is to be carried out.
- Regulatory status of the subject devices particularly in five GHTF founding member countries i.e. [European Union (EU), United States (US), Japan, Canada and Australia]
- Risk classification in Country of Origin as well as in five GHTF countries
- Technical Data submitted along with the application as per Annex II.



Technical Data Requirements

For all Class of Medical Devices

a. Design control/Analysis data

For physical and metrological standardization & compared with the predicate devices.

b. Biocompatibility Data

- Attributes to the biocompatibility analysis includes

- i. Contact of device with the body
- ii. Duration of contact with the body.
- iii. Protocol for carrying out study
- iv. Test conducted and
- v. Summary report.

a. Feasibility/Phase I Study

- i. Animal Study data which should include data on –
Performance, Safety and Absolute tissue reactions.

b. Pivotal/Phase II/III Study

- i. Animal Study data as provided before the start of feasibility study.
- ii. Human Clinical Research data generated from previous study

Note: For Active Medical Devices

If the active component is biochemical in action, its pharmacological data should be submitted as per Schedule Y



Comparison of Regulations

| Requirements | Current | Proposed |
|--------------------------|---|--|
| Application Requirements | <ul style="list-style-type: none">- Pharmacological Data- Toxicological Data- Composition of drug- Dosage Form- Chemical Name | <ul style="list-style-type: none">- List of accessories of devices- Variation in shape and size of device- Composition of devices- Biocompatibility |
| Protocol - Study Design | Blinded, Randomized, placebo studies | <ul style="list-style-type: none">- Randomized and Historical control- Single arm study |
| Approvals | Notification to DCG (I) | IRB, DCG (I) and Registration with CTRI |



Comparison of Regulations (contd.)

| Requirements | Current | Proposed |
|---------------------------|--|--|
| Quality standards | - cGMP | - ISO 13485 |
| Risk Classification | - Drugs specific | - COO and 5 GHTF Countries |
| Guidelines Followed | - Schedule Y in alignment with ICH/GCP | - Schedule Y - ISO 14155 - Directive 2001/20/EC and - Directive 2005/28/EC - Consequently ISO 14155 as proposed by GHTF projected to be followed |
| Trial Follow up timelines | - 6 months for devices with CE marking - 12 months for devices without CE marking | - N/A |
| ADR Reporting | Format used for drugs | Format used for drugs. |



Registration of CROs

- Draft guidelines and requirements for registration of CROs in the country have been developed.
- Proposed to be incorporated as new **Schedule Y1 to Drugs & Cosmetics rules, 1945**.
- Also proposed to incorporate **Rule 122DAB** for the proposed new schedule Y1.
- Proposal made for **Schedule Y1 to DTAB (Drug Technical Advisory Board)**



Clinical Trial Inspection Program

Guidelines published by CDSCO on its website on 1st Nov 2010

- **Objectives :**

- a. To verify GCP compliance to protect the rights, safety and well being of the subjects involved in clinical trial
- b. To verify the credibility and integrity of clinical trial data generated
- c. To verify the compliance with various regulatory provisions as per
 - Drugs & Cosmetics Rules

- **Purpose** is to provide direction to:

- Inspectors/CDSCO officers for conducting inspection of site of clinical trial,
- Sponsor / CRO's facilities involved in clinical trial and information to investigators, sponsor/ CRO'S about procedures for inspection and follow up of action.

Conclusion

- Regulatory control on Medical Devices are still in the budding stage in India.
- The regulatory requirements for trials have been framed based upon the proposed guidance ([Risk Based Classification](#)).
- The regulations for trial of devices has not been completely separated (combination products and active devices).
- The stepping stone has been laid, but we have a long way to go as far as technical and infrastructure expansion is concerned.





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