Regulations & Guidelines Specific to Ethics

Schedule Y & CDSCO-GCP

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CDSCO – West Zone

Outline

- Licensing Authority – India
  - Clinical Trial:
    - CDSCO Head Quarters, New Delhi
  - Marketing and Manufacture:
    - State Drug Control Organisation
- Recent Amendments in D & C Rules
- Other measures taken to strengthen CT regulation
- Conclusion

India-Well defined Drug Regulatory System

Government of India

Ministry of Health & Family welfare (Secretary, Health)

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DGHS

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CDSCO

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DCGI ← **DTAB**

- Enforcement & GMP Audit Div.
- Quality Control Division-DTL/CDL
- Registration Div.
- New Drugs Div.
- Pharmacovigilance
- Trainings

Ministry of Chemicals & fertilizers

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Department of Pharmaceuticals

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NPPA

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(Pricing of Drugs)

Ministry of Commerce

(Compulsory Licensing of Life saving category drug)

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Patent Office

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Controller General of patents

Ministry of Science & Technology

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DBT (RCGM)

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CSIR Labs

Ministry of Environment

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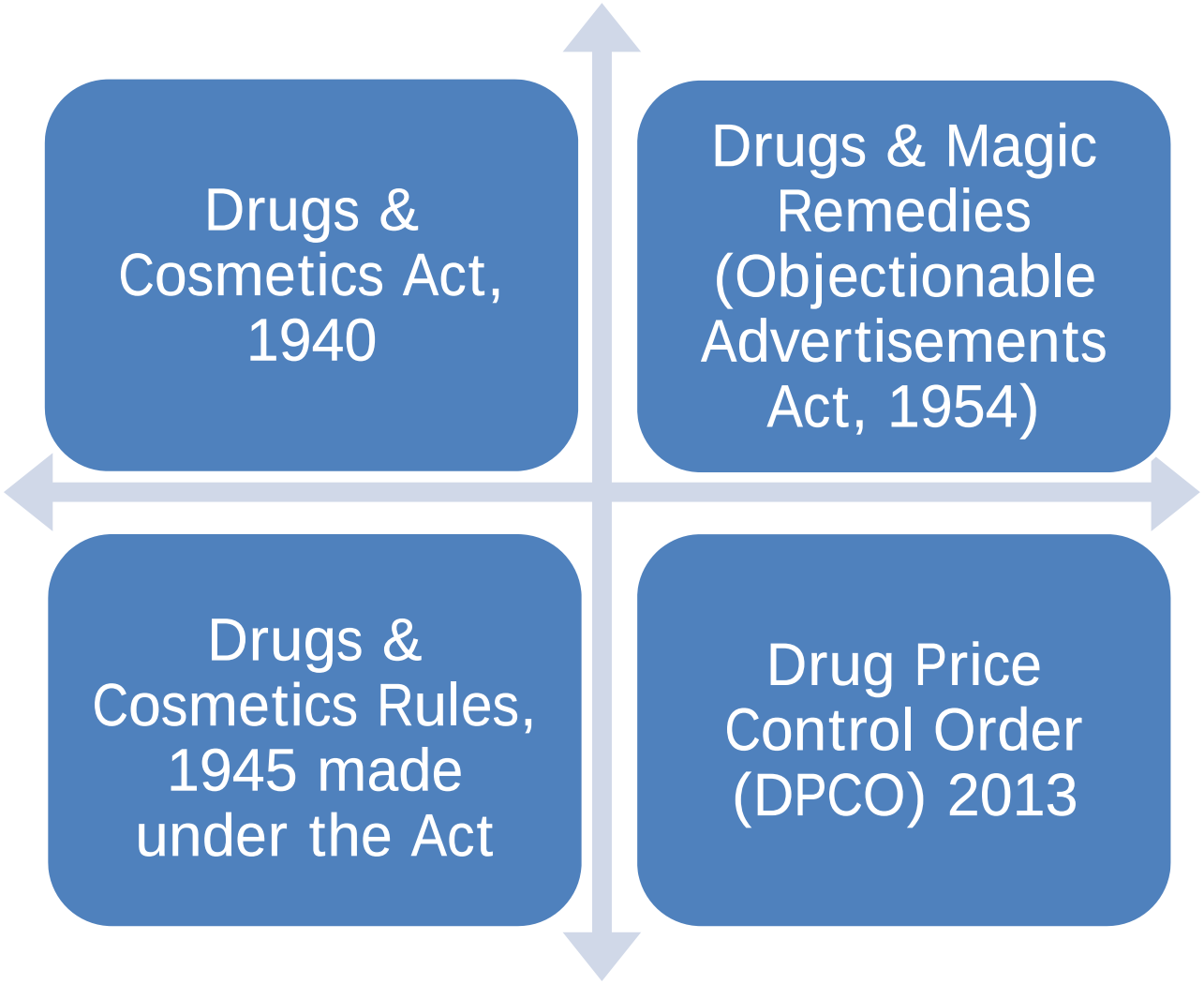
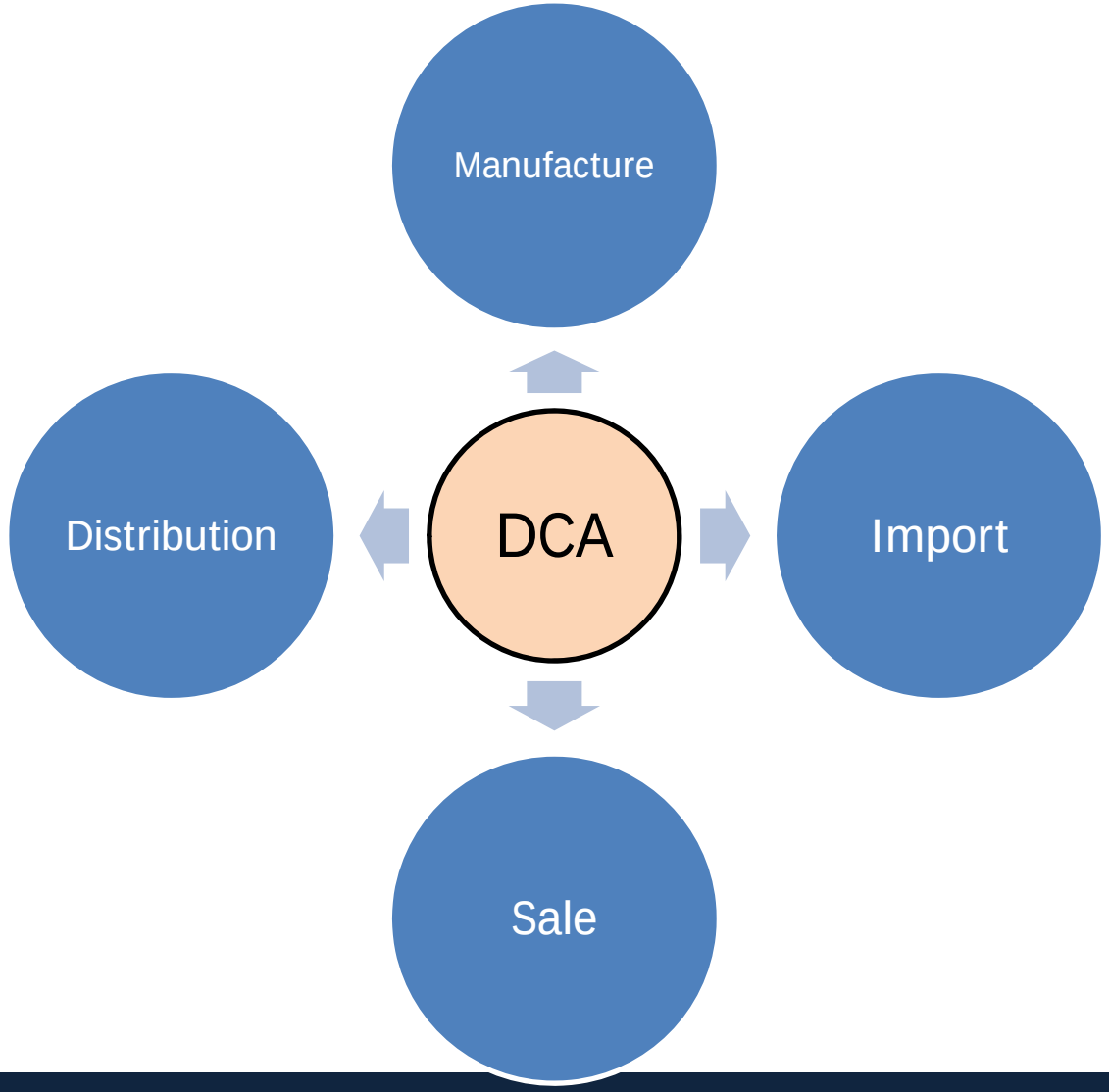
Environmental clearance to the manufacturing sites and recombinant drug products

(GEAC)

Legal Enactments to Regulate Import, Manufacture & Sale of Drugs



What is Regulated under DCA



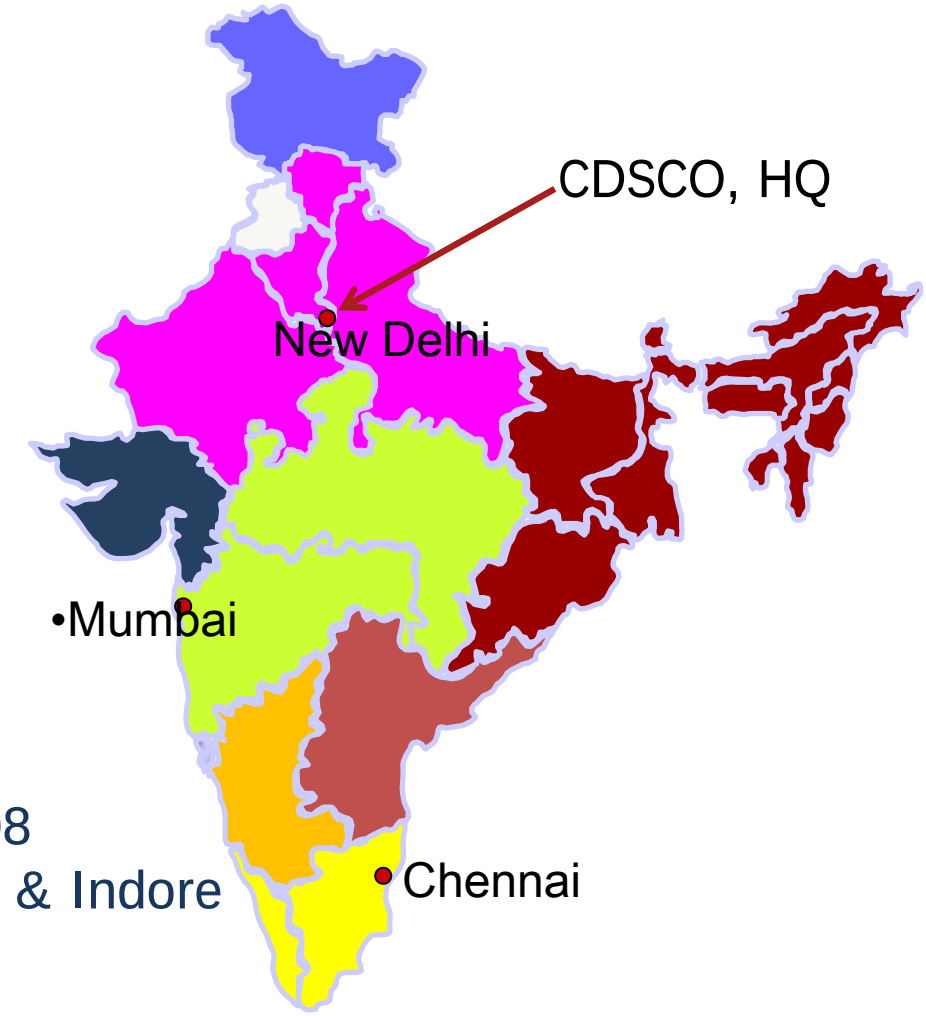
What is Regulated under Rules

Functions of CDSCO

- Approval of New Drugs and Clinical Trials
- Import Registration and Licensing
- Licensing of Blood Banks, LVPs, Vaccines, r-DNA products & Some Medical Devices
- Amendment to Drugs & Cosmetics Act and Rules
- Banning of Drugs and Cosmetics
- Grant of Test License, Personal License, NOCs for Export
- Testing of Drugs

CDSCO – Geographical location Zonal/ Sub-Zonal Offices (10)

- CDSCO North Zone (Ghaziabad)
- CDSCO West Zone (Mumbai)
- CDSCO South Zone (Chennai)
- CDSCO Zone (Ahmedabad)
- CDSCO Zone (Hyderabad)
- CDSCO Sub Zone (Bangaluru)
- CDSCO Sub Zone (Chandigarh)
- CDSCO Sub Zone (Jammu)
- CDSCO Sub Zone (Goa)



Port Offices/ Airports: 11, Laboratories: 08
Proposed Sub Zonal Offices(2): Guwahati & Indore
Proposed Port Office at Vishakhapatnam

Functions of State Licensing Authorities

- Licensing of Manufacturing Site for Drugs including API and Finished Formulation
- Licensing of Establishment for sale or distribution of Drugs
- Approval of Drug Testing Laboratories
- Monitoring of Quality of Drugs and Cosmetics marketed in the Country
- Investigation and prosecution in respect of contravention of legal provision
- Recall of sub-standard drugs

Approval of Clinical Trials, Import & Manufacture of New Drugs

Requirements and Guidelines - Schedule Y	
Rule 122 A	• Permission to import new drug • Definition of New Drugs: o New Substance having therapeutic indication o Modified or new claims, new route of administration for already approved drug o Fixed Dose Combination
Rule 122 B	Permission to manufacture new drug
Rule 122 DA	Application for permission to conduct clinical trials for New Drug/ Investigational New Drug.
Rule 122 DAA	Definition of Clinical Trial: o For the purpose of this Part, “Clinical Trial” means a systematic study of new drug(s) in human subject(s) to generate data for discovering and/or verifying the clinical, pharmacological (including pharmacodynamics and pharmacokinetic) and /or adverse effects with the objective of determining safety and / or efficacy of the new drug.]

Approval of Clinical Trials, Import & Manufacture of New Drugs

Continued

Requirements and Guidelines - Schedule Y	
Rule 122 DAB	• Compensation in case of injury or death during clinical trial (G.S.R. 53(E) dated 30th January 2013). • G.S.R. 889(E) dt.12-12-2014; Clarifications on the criteria for eligibility of compensation (Will be implemented 6 months from the date of publication).
Rule 122 DAC	Permission to conduct Clinical trial.(G.S.R. 63 (E) dated 1st February 2013).
Rule 122DB	Suspension or cancellation of Permission/ Approval.
Rule 122 DD	Registration of Ethic Committee, (G.S.R. 72 (E) dated 8th February 2013).
Rule 122 E	Definition of New Drugs

What is Schedule Y

- Under Part X-A of Drugs & Cosmetics Rule 1945
- Describes information/ data required for *Approval in Clinical Trial and/or to Import or Manufacture of New Drug for Marketing in India*
- Outlines extensive study criteria in line with the globally accepted formats such as ICH Guidelines and US-FDA Regulations

Salient Features of Schedule Y

- Concurrent phase global clinical trials permitted
- Phase I (first-in-human) study of New Drug substance discovered outside the country, not permitted (Repeat Phase I is permitted)
- Stipulates responsibilities of EC, Investigators and Sponsor
- Structure, contents and formats for CT protocols, reports, EC approvals, ICF, SAE reporting are incorporated
- There are 12 Appendices
- Provides statutory support to CDSCO-GCP Guidelines & ICMR-Ethics Guidelines for Biomedical Research

What is GCP?

- International ethical and scientific quality standard for:
  - Designing
  - Conducting
  - Recording
  - Reporting

Trials that involves participation of human subjects

Why GCP ?

- Legal Requirement
  - Protects the rights, integrity & confidentiality of research subjects
  - Provides assurance that the data & results are credible & accurate
  - Global Acceptance

Ethics Committee Registration:

- As per Gazette Notification No. GSR 72 E dated 8th Feb 2013, and under **Rule 122DD**

  "No Ethics Committee shall review and accord its approval to a clinical trial protocol without prior registration with the Licensing Authority as defined in clause (b) of Rule 21", (i.e. DCG(I))

- Ethics Committee shall review and accord its approval to clinical trial and also carry on-going review of a trial as specified in Schedule Y and GCP guidance document.

Ethics Committee Registration

- EC shall review and accord its approval to clinical trial and also carry on-going review of a trial as specified in Schedule Y and GCP guidance document.
- In case of any Serious Adverse Event (SAE) occurring to the clinical trial subject during the trial, the EC shall analyze and forward its opinion as per procedure specified in APPENDIX –XII of schedule Y.
- In said rules, in Schedule Y, in APPENDIX-VIII relating to Ethics Committee.

E.C. Registration:
Common Deficiency in the Application

- Under which authority EC is formed ?
- Undertaking in CDSCO Format
- Completion of 19 point check-list given by CDSCO
- All Standard Operative Procedures (SOPs)
- Mainly SOPs for Vulnerable Population
- Proper dossier with page numbers
- Request for Ethics Committee registration under rule
- 122 DD of Drugs & Cosmetics Rules
- Brief about Hospital / Trial Site.

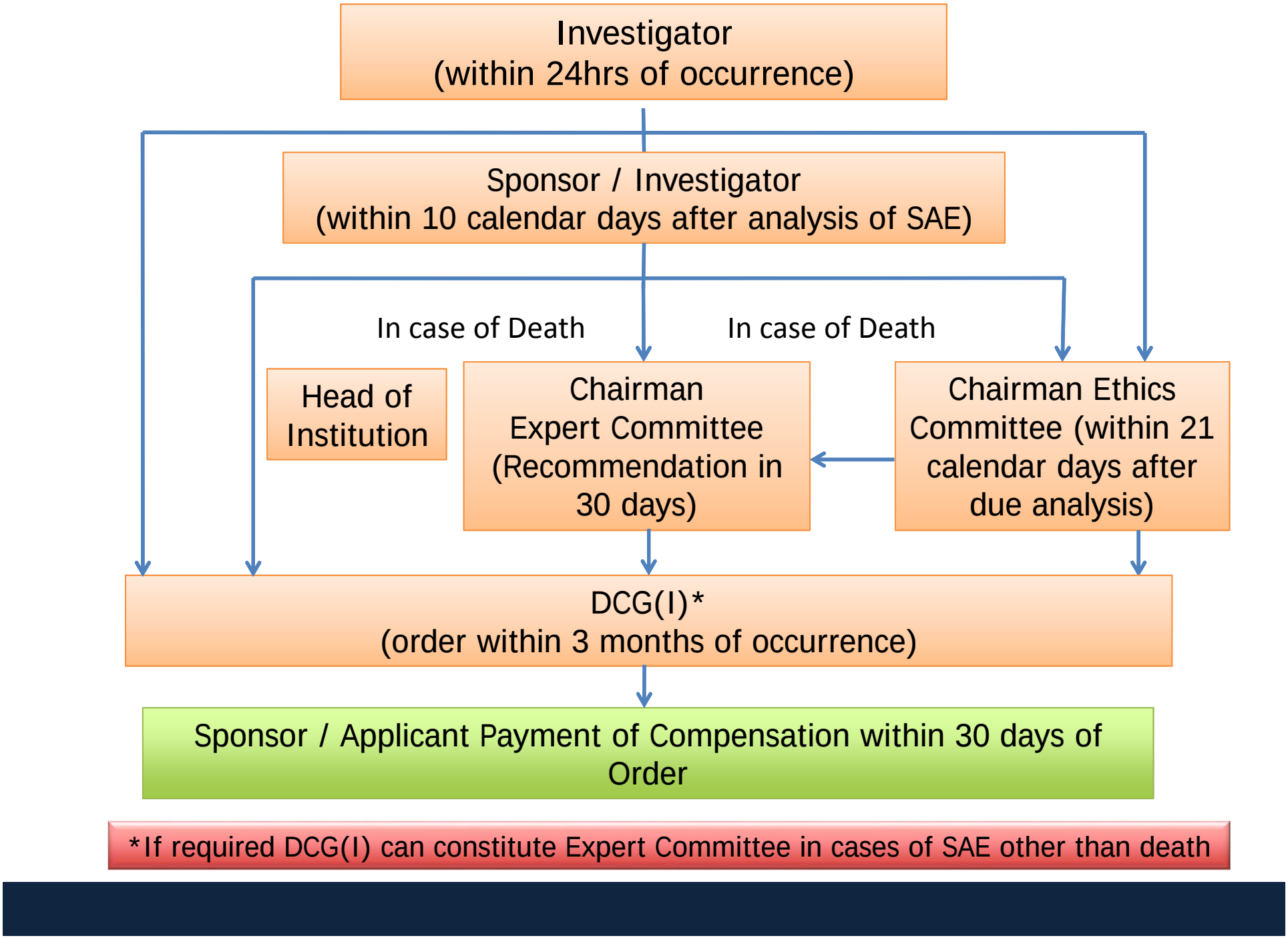
SAE Reporting (Rule 122 DAB)

- All serious and unexpected adverse events should be reported by P.I. to CDSCO, Sponsor and EC within 24 hrs (earlier 24hrs reporting was limited to sponsor by PI)
- The detailed report of SAE after due analysis, should be forwarded by PI & Sponsor to chairman of EC, CDSCO and Head of Institution within 10 calendar days of occurrence of SAEs (the SAEs of death also needs to be forwarded to the Chairman of Expert Committee appointed by CDSCO.)
- SAE reports submitted to the CDSCO should be in COLOR coded binding:-

  RED: SAEs or Deaths,

  Blue: SAEs due to Injury,

  Remaining cases of SAEs in White cover.


Investigator
(within 24hrs of occurrence)
Sponsor / Investigator
(within 10 calendar days after analysis of SAE)
In case of Death
In case of Death
Head of Institution
Chairman Expert Committee (Recommendation in 30 days)
Chairman Ethics Committee (within 21 calendar days after due analysis)
DCG(I)*
(order within 3 months of occurrence)
Sponsor / Applicant Payment of Compensation within 30 days of Order
*If required DCG(I) can constitute Expert Committee in cases of SAE other than death

Formula on Quantum of Compensation

Compensation = BxFxR/ 99.37

B= Base Amount (8 lakhs)

F= Factor depending on age (Workmen Compensation Act)

R= Risk Factor (severity & seriousness, co-morbidities etc. 0.5-4.0)

Sr No	Age	F (factor)	Compensation amount (in Rupees lakhs)				
			R = 4	R =3	R =2	R =1	R = 0.5
			Healthy volunteers	Pt with mild risk	Pt with moderate risk	Pt with high risk (survival 6-24 months)	Terminally ill pt (survival NMT 6 months)
1	20	224.00	72.13	54.10	36.06	18.03	9.01
2	25	216.91	69.85	52.38	34.92	17.46	8.73
3	30	207.98	66.97	50.23	33.48	16.74	8.37
4	35	197.06	63.45	47.59	31.72	15.85	7.93
5	40	184.17	59.30	44.48	29.65	14.82	7.41
6	45	169.44	54.55	40.92	27.28	13.64	6.82
7	50	153.09	49.29	36.97	24.64	12.32	6.16
8	55	135.56	43.65	32.74	21.82	10.91	5.45
9	60	117.41	37.80	28.35	18.90	9.45	4.72
10	65	99.37	32.00	24.00	18.00	8.00	4.00

State-Wise List of Ethics Committee Registered By CDSCO (Total 745)

Andhra Pradesh	80
Assam	03
Bihar	04
Chhattisgarh	01
Delhi	48
Goa	04
Gujarat	86
Haryana	09
Himachal Pradesh	02
Jammu & Kashmir	01
Karnataka	75
Kerala	48

Madhya Pradesh	09
Maharashtra	178
Mizoram	01
Orissa	10
Puducherry	04
Punjab	14
Rajasthan	24
Sikkim	02
Tamilnadu	70
Uttarakhand	02
Uttar Pradesh	32
West Bengal	38

Clinical Trials Registration (CTRI)

To enhance:

- Transparency
- Accountability &
- Accessibility of clinical trials,

- Made mandatory by the DCGI's office from June 15, 2009.
- 20 data set points of the WHO, as well as details of India Investigators, ethics and DCGI approval (including submission or approval documents)
- For Global clinical trials, specific information regarding the number of patients being recruited and the date of first enrollment in India
- www.ctri.nic.in

Other Regulations and Office Orders

- Ancillary care for any other illness afflicting patients in a clinical trial
- Clinical trials must be conducted in accredited site after review by accredited (and registered) IRB/REC, and only involving certified (accredited) investigators
- Clinical investigators may participate in no more than three clinical trials at any one time
- 50% of clinical trials must be performed in public hospitals with over 50 beds Every informed consent must be video-recorded by a videographer and preserved

Certification and Accreditation

- Quality Council of India chosen as central agency in charge of standards and accreditation, including defining process and inspections
- QCI published draft standards, posted on National Accreditation Board for Hospitals & Healthcare Providers (NABH):

  http://nabh.co/Notice_draft_accreditation_standards.aspx#sthash.ZFPCfUxD.dpuf

India: Still Pending

- Requirement for placement of trials in 50-bed hospital
- Compensation revisions for situations not modified (e.g. Phase 4 trials, post-marketing surveillance, non-compliance)
- Compensation formula for injury
- Definition of “ancillary care” expectation for inter-current illness during clinical trial
- Structure, education and training of regulatory authorities
- Elevation of CDSCO/DCGI to higher authority and status in government
- Increased investment in regulatory offices and competence of officials Transparency of regulatory processes and decisions

Conclusion

- Clear understating of Mandate, Rules & Regulations of:
  - Training to all EC members
  - Accreditation/Registration by QCI
  - Integrity of approvals
  - Audit/ Inspection of CT sites
  - Action against violators

Thank You


CDSA


thsti
Translational Health Science
and Technology Institute