REGULATORY RESPONSE TO COVID-19

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Outline

- Summarizing various regulatory response as notices, guidelines, fast track approval
- What are the regulatory enablers
- New Drug and Clinical Trial Rules- Salient Points
- Medical Device Rules 2017-Salient Points
- Current Regulatory Pathway
- Approval Process of New Drug
- Regulatory pathway example-rDNA vaccine
- Regulatory pathway of fast track approval
  - requirements of licensure
- Lessons learnt

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- India initiated the required preparedness and action much before advice of WHO declaring the outbreak of coronavirus as public health emergency and subsequently as pandemic including assessment of whole supply chain for the essential medicines and PPE kits

- Issues taken up with the State Government as well as various drug manufacturing associations to ensure that the manufacturers have enough stock of APIs and formulation and there is adequate supply and no shortages of essential medicines.

- Government has issued advisory to all the State/UT Governments to ensure that merchant importers/stockists as well as indigenous manufacturer of APIs do not hoard and create artificial scarcity of APIs/KSMs in the country.

- Various public notices and communication/request letters issued by CDSCO to the state/UT Drugs Controllers

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- Notice for the stakeholders indicating modalities & pathway for fast track approval of all product for COVID-19 clinical trial /approval of new drugs including vaccines, rDNA derived products and in-vitro diagnostic kits
- Any firm having a Drug/Vaccine under development for COVID-19 can directly approach DCG(I) through Public Relation Office for seeking guidance for regulatory pathway.
- Any firm or research institute having protocol for repurposing of existing drugs/vaccines for treatment of COVID-19 will also be given priority for review and approval.
- Applications for Clinical Trial permission and applications to import or manufacture Drug/Vaccine for sale and distribution would be processed on priority though expedited review/accelerated approval.
- Any firm having Drug/Vaccine already approved for COVID-19 in any other country can directly approach DCG(I) through Public Relations Office regarding expedited review/accelerated approval for marketing in India.

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- Data requirement for animal toxicity study, clinical study, stability study etc. may be abbreviated, deferred, or waived on case to case basis depending upon the type of vaccine, nature of drug, plant from which the drug is extracted & its experience in case of Phyto-pharmaceutical.
- Applications to manufacture or import Drug/Vaccine for test, analysis and further use BA/BE or Clinical Trial to be processed within 7 days.
- Grant of Import license (Form 10) without Registration Certificate (Form 41) in case of emergency, subject to approval of Central Government for sale or distribution after completion of clinical trial and grant of manufacturing approval by CDSCO.

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- For ensuring accessibility port offices have been directed to release consignments of vaccines, critical in-vitro diagnostics and blood products (which are usually sampled 100% for testing) based on the review of the documents, protocol, certificate of release of batch by the manufacturer and satisfactory history of the product subject to certain conditions.

- Circular issued for lot release by CDL, Kasauli for Human vaccines manufactured domestically by review of summary lot protocol on case by case basis with condition that the manufacturers shall send the samples as per usual procedures to CDL, Kasauli for evaluation until logistics restored

- Request for fast track approval of Hand Sanitiser Manufacturing License in 3 days by SLA

- Grant of permission for industrial oxygen manufacturer to manufacture oxygen within 24 hours by States.

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- Revised Regulatory Guidance on conduct of clinical trial
- understanding the various challenges that may arise during conduct of clinical trial in this pandemic outbreak which may lead to difficulties to maintain
- complete adherence to the approved protocol,
- regulatory provisions/ procedures and applicable guidelines in respect of various activities involved in conduct of clinical trial
- including recruitment of trial subjects, laboratory testing, diagnosis, administration of investigational product, reporting of SAEs, scheduled visits, assessment of safety and efficacy parameters, etc.
- Such impact on conduct of clinical trial will vary depending on nature of trial, disease condition, locality/region where the trial site is located, government restrictions including that of local administration etc.
- Electronic mode of communication by email between sponsor, ethics committee, investigator and to the regulatory authority as notification

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- Monitoring the availability of essential drugs including 55+97 critical drugs required for treatment and management of the patients infected with COVID-19 and to take necessary measures to ensure their availability on regular basis
- Gazette notification for stockpiling of vaccines under clinical trial was published.
- Considering the emergency and unmet medical need, CDSCO has approved three drugs for Restricted Emergency Use in the country for treatment of COVID-19 infection:

What are the regulatory enablers?

Various measures for streamlining the Rules/Regulations, review Process and other regulatory activities:

- New Drugs and Clinical Trial rules 2019
- Medical Device Rules 2017
- E-governance
- Checklist for submission of applications, review
- Prescribed timelines for various activities
- Guidelines, FAQs, Notices etc., for streamlining the regulations
- PRO for regulatory guidance to start-ups/innovators , grievance redressal, response to query of applicants

New Drug & Clinical Trial Rules, 2019-Salient Points

- Standards as per global best practices for Safety & efficacy evaluation
- Expansion of definition of new drug
- Time bound disposal of applications
- Provision of deemed approval of Clinical Trials of indigenously developed new drugs molecules
- Accelerated approval and waiver
  - Severity, rarity, or prevalence and
  - the availability or lack of alternative treatments
  - meaningful therapeutic benefit over the existing treatment.
- Expedited review

New Drug & Clinical Trial Rules, 2019 - Salient Points

- Compensation
- Pre-submission and post submission regulatory guidance
- Post-marketing safety assessment
- Expert Committees
- Orphan drugs intended to treat a condition which affects not more than five lakh persons in India
- Separate Provisions for Registration of Ethics Committee for regulatory submission and Biomedical research

Medical Device Rules 2017-Salient Points

- Effective from 01.01.2018
- To regulate the Clinical Investigation, Manufacture, Import, Sale and Distribution of the medical devices
- Harmonised with the international regulatory practices and provide comprehensive legislation for the regulation of Medical Devices
- Risk based classification
- Provisions of Notified Bodies

Medical Device Rules 2017-Salient Points

- Quality Management System in line with ISO 13485 has been adopted;
- Provisions related to the ‘Essential Principles of Safety and Performance’ for manufacturers have been specified in the Rules;
- Separate provisions for regulation of Clinical Investigation/ performance of investigational medical devices (i.e. new devices)/In-vitro Diagnostic Kits have been made at par with international practice.
- Provision is made to designate or establish Central Government medical device testing laboratories to verify conformance with the quality standards.

Current regulatory pathway

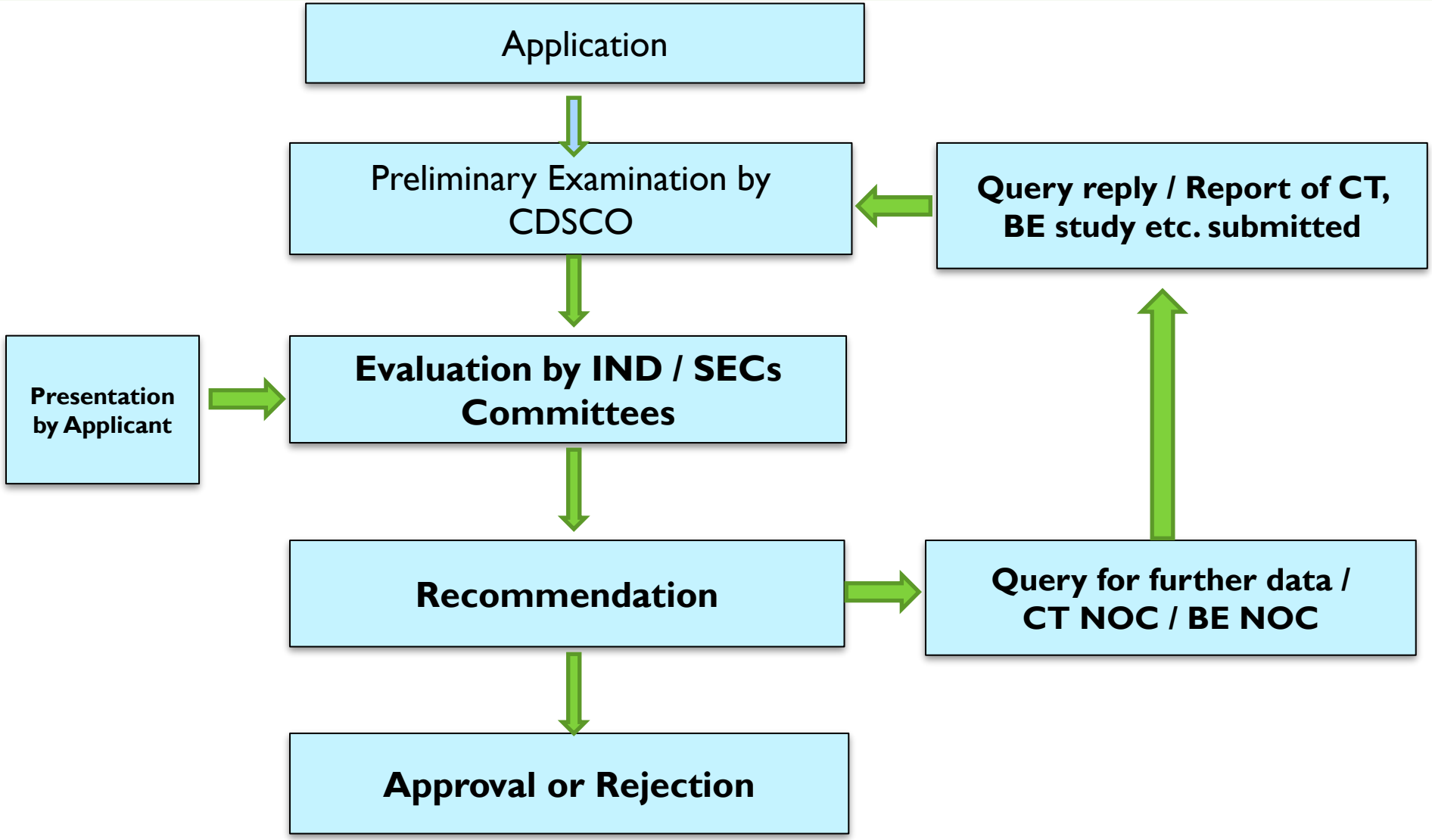
Domestic

- Permission to manufacture for test & analysis or for Clinical trial.
- Permission to conduct clinical trial
- Permission to manufacture for sale & distribution (Market Authorization)
- Manufacturing License for sale & distribution

Imported

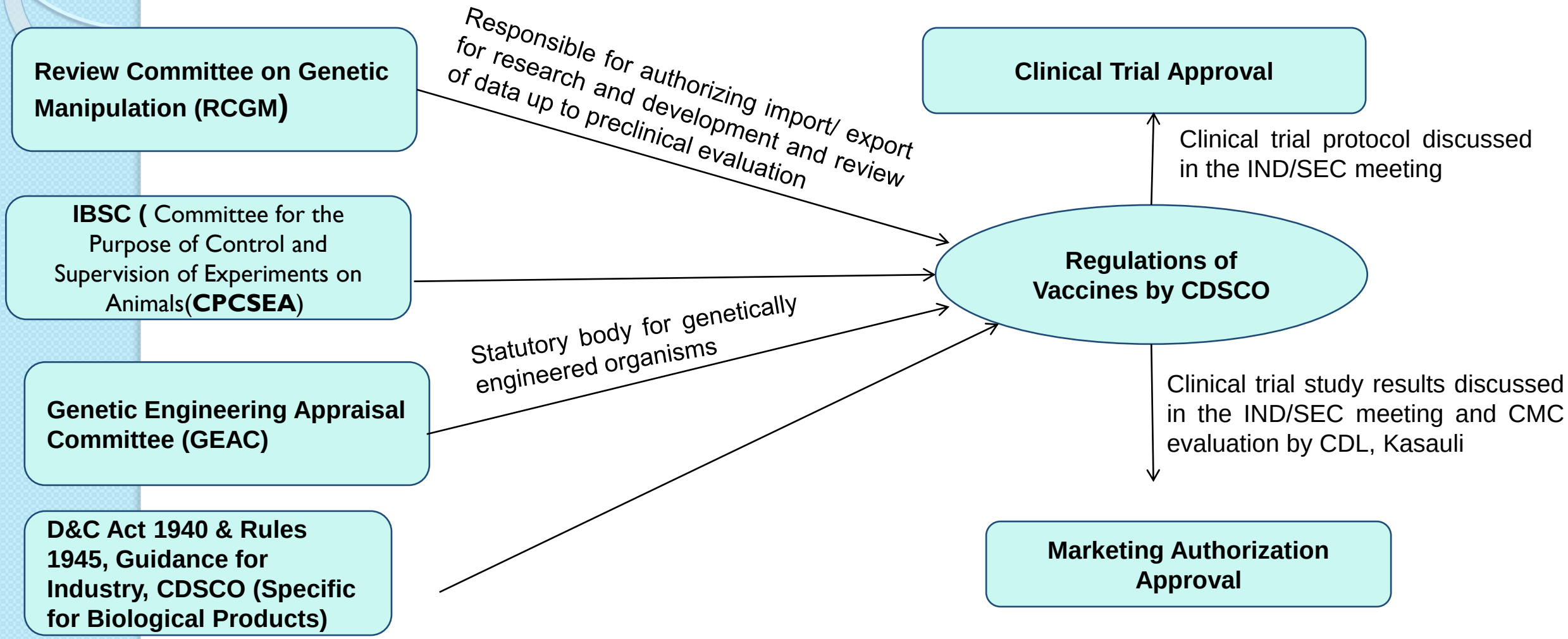
- License to import for test & analysis or for Clinical trial
- Permission to conduct clinical trial
- Permission to import for sale & distribution (Market Authorization)
- Registration & import license

Approval Process of New Drug



Regulatory pathway example- rDNA Vaccine

Diagrammatic Regulatory pathway for the approval of rDNA Vaccine



Approval Process of New Drug

Second Schedule of NDCT Rules 2019

Data required

- Chemical and Pharmaceutical information (including stability study, impurity profile etc.)
- Pre- Clinical data (Animal Pharmacology/ Toxicology etc.)
- Clinical Data (Phase I,II,III etc.)
- Regulatory Status in other country (approval/ withdrawal)
- COPP/FSC (in case of import)
- Label, PI

Regulatory Pathway for fast track review or approval

Accelerated Approval Process
Consideration of surrogate endpoint rather than using standard outcome measures Approval with a condition to conduct post marketing trials Consideration of efficacy in Phase II clinical trial with a defined dose.

Quick or Expeditious review process

• Where the evidence for clinical safety and efficacy have been established but drug has not completed the all or normal clinical trial phases with following:
  • Preclinical data makes a case for claimed efficacy
  • Where there is no established management or therapeutic strategy available as on date

Requirements for Licensure

Pre-Clinical Studies	Single-dose toxicity studies: • In 2 rodent species (mice and rats) using the same route as intended for humans. • Animals should be observed for 14 days after the drug administration, and Minimum Lethal Dose (MLD) and Maximum Tolerated Dose (MTD) should be established. Repeated-dose systemic toxicity studies: • In at least two mammalian species, of which one should be a non-rodent. . • 28 Days study can be acceptable in vaccine. Dose- ranging study: • Identification of target organ of toxicity and establishment of Maximum Tolerated Dose (MTD) for subsequent studies.

Requirements for Licensure

Clinical Studies	• Based on data generated in clinical trial where surrogate endpoint may be considered • These should be measurable earlier than irreversible morbidity or mortality (IMM) and reasonably likely to predict clinical benefit
Chemistry, Manufacturing & Control (CMC)	Product & Process Characterization: • With Critical Quality Attributes (CQA) & Critical Process Parameters (CPP). • High quality development of Assay • Reference standards development & qualification Stability: • long term stability data using Risk based approach • Mechanism/strategy to extend shelf life Consistency(vaccines) : Pre-Marketing commitment to reproduce and release consistency lots.
Regulatory	• Inspection of manufacturing site. • Lot Release by Central Drugs Laboratory, Kasauli(vaccines)

Lessons Learnt

- Rapid response through fast track approval process without compromise to quality, safety, efficacy - rolling reviews and going ahead subsequently
- Working in co-ordination with various Govt department, relevant ministries, scientific institution, scientist and research communities , expert group, international regulatory agencies, WHO etc
- Benefit-risk assessment
- Post marketing assessment
- Government has assessed and ensured the availability of the essential medicines, hand sanitizers as well as protective equipment's including masks, PPE Kits, medical oxygen as well as fast track processing of applications for clinical trials and new drug including vaccines for COVID and taken all possible measures to meet the public health emergency for COVID.

THANK YOU