Highlights of "New Drugs and Clinical Trials Rules 2019"

INTRODUCTION

Ministry of Health and Family Welfare [MoHFW] has notified the "New Drugs and Clinical Trials Rules, 2019" on 25th March 2019 [Ref Ministry of Health GSR Notification #227 dated 19 March 2019]. The new rules aim to promote clinical research in the country and will change the regulatory landscape for the approval of new drugs and conduct of clinical trials in the country.

EFFECTIVE DATE

25 March 2019 [date of publication on eGazette website]. Chapter IV which includes provision for 'Ethics committee for biomedical and health research' will be effective after 180 days i.e. **21 Sep 2019**.

APPLICABILITY

The rules will apply to all new drugs, investigational new drugs for human use, clinical trial, bioequivalence study, bioavailability study and Ethics Committee. The new rules will supersede Part XA and Schedule Y of Drugs and Cosmetics Rules, with immediate effect. If there is any inconsistency between these rules and any other rule made under the Drugs & Cosmetics Act, the provisions of these rules shall prevail over such other rules. Actions taken according to the existing rules [Drugs & Cosmetics Rules, 1945] shall continue to be in effect and valid. This means existing licenses, orders, directions will continue to remain valid.

FEES & FORMS

- A hiked fee structure has been implemented. Key ones being :
  - 3 lakh INR (aprox 3800 Euro/4500 USD) for Phase I
  - 2 lakh INR (aprox 2500 Euro/2900 USD) for Phase II, III, IV & BA/BE study
  - 5 lakh INR (aprox 6500 Euro/7200 USD) for pre submission meeting
  - 50,000 INR (aprox 650 Euro/720 USD) for post submission meeting
  - 5 lakh INR (aprox 6500 Euro/7200 USD) for registration of BA / BE study centre
  - 5 lakh INR (aprox 6500 Euro/7200 USD) for new drug permission / Finished formulation or API [import]

- Administratively, all the application and approval formats have undergone a change. Some of them are :
  - Form CT04 – Clinical Trial Application Form (Replaces Form 44)
  - Form CT 04 A- Automatic Approval Information to CDSCO
  - Form CT 06 - Permission to Conduct CTs by CDSCO
  - Form CT 16- Application to grant of License to Import of New Drug for Clinical Trials (Replaces Form 12)

SALIENT FEATURES

- **Definitions** of many previously undefined terms have been included. New drug definition has been broadened, covers newer therapeutic options like SR/MR, NDDS, Living modified organisms, monoclonal antibodies, stem cells derived products, gene therapeutic products, xenografts etc.

- Defines orphan drug in the regulation as drug used to treat condition which affects not more than 5 lac persons in India

- **Provision of waiver of local ph III clinical trials** if drug is approved and marketed in certain countries [as notified from time to time] subject to certain conditions and confirming conduct of Phase IV study. The Ph IV study requirement could be reduced in case of drugs of special relevance, in case of unmet need, for rare disease for which drugs are not available or available at a high cost or orphan drugs

- Animal toxicology, reproduction studies, teratogenic studies, perinatal studies, mutagenicity and carcinogenicity studies may be modified and relaxed in case of imported products if new drug is available for more than **2 years in certain countries**. In case of locally manufactured product, this relaxation may be allowed if the drug is marketed in other countries for **several years.**

- **Provision of Pre-submission meetings included** – Applicants can discuss their projects with the regulators and subject experts by paying a certain fee, before making actual submission to the regulator, for seeking guidance about the requirements of law and procedure applicable for their projects.

- **Provision of Post-submission meetings included:** If the applicant desires to seek clarification in person in respect of pending application and queries related thereto, the applicant may make an application for a post-submission meeting with the officer designated by the Central Licencing Authority within a period of **fifteen days** from the date the query was received for seeking guidance with regards to the queries concerning pending application.

- **Provision of Post-Trial Access**
    - If the drug is beneficial, and there is no alternative therapy, Investigator can recommend post trial access for the patient
    - EC approval and Patient/legal heir's consent is required
    - No liability on sponsor for post-trial use by patient

- **Validity of clinical trial permissions**
  The permission to initiate Clinical Trial will be valid till 2 years from the date of issue, unless extended by licensing authority

- **New provisions to be followed during trial**
    - Enrolment status should be submitted on quarterly basis to licensing authority
    - Six monthly status reports on the trial should be submitted in SUGAM portal
    - Early termination of clinical trial should be reported to licencing authority within 30 working days
    - In case of study related injury or death, compensation should be provided within 30 calendar days of receipt of orders from licencing authority [*previously this was 30 days*].
    - If a drug is found to be useful in clinical development, firm should submit application for import or manufacture of the drug for sale in India, unless otherwise justified.

- SAE reporting timeline for sponsor changed to 14 calendar days from "awareness of SAE/Death" and not "Occurrence/onset of SAE"

- **Compensation for injury or death**
  No change in regulation;
  Central licensing Authority at their discretion may or may not constitute the Expert Committee to review reports of SAE submitted. In case they don't decided to formulate the committee, then the Central Licensing Authority shall review the report and convey the decision

- **Provisions for BA / BE studies are more clearly defined**
  Provisions like application process, inspection process, suspension or cancellation of permission etc are defined clearly in the new regulations.
  Requirements of BA / BE centers registrations have been defined in the new rules
  BE Permission will remain valid for a period of **one year** from the date of its issue, unless suspended or cancelled by the Central Licensing Authority

- Requirements for Clinical Trial labels are defined under "Manner of labelling" and in addition to routine contents, name of institute where clinical trial is proposed to be conducted is required to be added

- Differentiation of Phase IV and Post marketing studies is described.
  - **Phase IV (Post marketing trial) is expected to be conducted a**pproved protocol with definite scientific objectives, inclusion/ exclusion criteria, safety/ efficacy assessment in approved indication in approved patient population. All ethical guidelines including Compensation rule needs to be followed and drug may be given free of cost.
  - Post Marketing Surveillance or observational or non-interventional study for active surveillance is expected to be conducted with approved protocol with scientific objective, Inclusion/ exclusion as per approved pack insert and regulatory provisions or guidelines of clinical trial are not applicable.

TIMELINES

Time bound approvals:

- Decision to grant of permission to conduct clinical trial of new drug or investigational new drug will be taken within 90 days.
- For clinical trial of drugs discovered in India / research and development done in India and the drug is proposed to be manufactured and marketed in India, application shall be processed within 30 working days. If no response from Licensing Authority is received in 30 working days then this application is deemed as approved.

  The applicant who has taken deemed approval shall before initiating the clinical trial, inform the Central Licensing Authority in Form CT-4A and the Central Licensing Authority shall on the basis of the said information, take on record the Form CT-4A which shall become part of the official record and shall be called automatic approval of the Central Licensing Authority

- For clinical trials of drugs already approved outside India, application will be processed within 90 working days. There is no provision of deemed approval.
- New drug approval in 90 working days [import as well as local manufacturing]

ETHICS COMMITTEE

- Composition : 50 percent of its members who are not affiliated with the institute or organization in which such committee is constituted.
- EC registration certificate shall be granted in Form CT-02 with in a period of 45 working days.
- Validity will be for a period of five years from the date of its issue, unless suspended or cancelled by the Central Licensing Authority
- Renewal of EC Registration: Ethics Committee may make an application for renewal of registration 90 days prior to the date of the expiry of the registration to ensure deemed continuity.
- Where a clinical trial site does not have its own Ethics Committee, clinical trial at that site may be initiated after obtaining approval of the protocol from the Institutional Ethics Committee of another trial site; or an independent Ethics Committee. The approving Ethics Committee shall be responsible for the study at the trial site which should be located within the same city or within a radius of 50 km of the clinical trial site.

REJECTION & APPEAL

In case of rejection, the applicant may request the Central Licensing Authority, to reconsider the application within a period of **sixty working days** from the date of rejection of the application on payment of fee and submission of required documents.

An applicant who is aggrieved by the decision of the Central Licensing Authority under the Ministry of Health and Family Welfare, may file an appeal before the Central Government within **forty-five days** from the date of receipt of such decision and the Government, may, after such enquiry, and after giving an opportunity of being heard to the appellant, dispose of the appeal within a period **of sixty days**.

SUSPENSION / REVOCATION

Provision of putting order of suspension or revocation in public domain:

In case, the Central Licencing Authority issue any order of suspension or revocation or cancellation of any permission or licence or registration granted under these rules, such order shall be made available in the public domain immediately by uploading it in the website of Central Drugs Standard Control Organisation.