DOCUMENTS TO BE SUBMITED FOR APPROVAL OF ADDITIONAL PRODUCT UNDER DRUG LICENSE GRANTED

1. Application (statutory) in Form-24 /27/31/24B/24A/27A/27D/27DA/31A

   duly signed by the Proprietor / Managing Partner / Managing Director/ Person declared as responsible under Sec.34 / Person Authorized by the Board of Directors accompanied by Company Board Resolution

2. Consolidated list of Formulations with packing particulars under each licence separately category wise viz. Tablets, Capsules, Injectables etc.

PRODUCT INFORMATION IN RESPECT OF

Bulk Drugs/ Formulations:

i. Brief Manufacturing procedure of each product

ii. Biopharmaceutical Classification System (BCS) class of the constituent API in case of Oral Dosage Forms and the results of bioequivalence study referred to in Schedule Y for Oral Dosage Forms containing drugs specified under category II and category IV of the Biopharmaceutical Classification System. (Results has to be submitted as per **Annexure-I**) (as per amendment to the Drugs and Cosmetics Rules, 1945 vide G.S.R. 327(E) dated: 03-04-2017)

iii. **evidence and data justifying that the applied drugs:**
(i) contain the constituent ingredients in therapeutic/prophylactic quantities as determined in relation to the claims or conditions for which the medicines are recommended for use or claimed to be useful.
(ii) are safe for use in the context of the vehicles, excipients, additives and pharmaceutical aids used in the formulation and under the conditions in which the formulation for administration and use are recommended;
(iii) are stable under the conditions of storage recommended; **(adequate evidence and data regarding stability has to be submitted)**
(iv) contain such ingredients and in such quantities for which there is therapeutic justification. (as per amendment to the Drugs and Cosmetics Rules, 1945 vide G.S.R. 360(E) dated: 10th April, 2018)

iv. Flow Chart with structural Formula of reactions (for bulk drugs) as per Master Formula record and specifications & analytical procedure of applied products with in-house specification claim.

v. Copies of monographs for formulations with pharmacopoeial specifications other than IP.

vi. Form 46/ Form 46-A in case of 'New Drugs' under Rule 122E of Drugs and Cosmetics Act and Rules made thereunder/ NOC from CDSCO for specific quantity export of New Drugs.

vii. Declaration regarding the Brand Names of the Product. **(in case of Formulations ONLY for Export).**

Note: (maximum no. of products in an application – thirty (30).

Annexure-I

Contents of the Bioequivalence Report /Checklist of Documents

- Results of bioequivalence study referred to in Schedule Y, along with the application for grant of a licence of oral dosage form of drugs specified under category II and category IV of the Biopharmaceutical Classification System (BCS).
- Bioequivalence report should give the complete documentation of its study protocol, conduct and evaluation.
- ***The BE study report should include (as a minimum) the following information:***

1. Table of contents
2. Title of the study
3. Names and credentials of responsible investigators
4. Signatures of the principal and other responsible investigators authenticating their respective sections of the report
5. Site of the study and facilities used
6. The period of dates over which the clinical and the analytical steps were conducted
7. Names and batch numbers of the products compared
8. A signed declaration that this was identical to that intended for marketing
9. Results of assays and other pharmaceutical tests (eg. Physical Description, dimensions, mean weight, weight uniformity, comparative dissolution etc.) carried out on the batches of products compared.

10. Full protocol for the study including a copy of Informed Consent Form (ICF) and criteria for inclusion/ exclusion or withdrawl of subjects.
11. Report of protocol deviations, violations
12. Documentary evidence that the study was approved by an independent ethics committee and was carried out in accordance with GCP/GLP.
13. Demographic data of subjects
14. Name and addresses of subjects
15. Details and justifications for protocol deviations
16. Details of drop outs and withdrawals from the study should be fully documented and accounted for.
17. Details of analytical methods used, full validation data, quality control data and criteria for accepting or rejecting assay results.
18. Respective chromatograms covering the whole concentration range for all, standard and quality control samples as well as specimens analysed.
19. Sampling schedules and deviations of the actual times from the scheduled
20. Details of how pharmacokinetic parameters were calculated
21. Documentation related to *statistical analysis*:
    i. Randomization schedule
    ii. Volunteer wise Plasma concentration and time points for test and reference products
    iii. Volunteer wise AUC_{0-t}, $AUC_{0-\infty}$, C_{max} , T_{max}, K_{el} and $t_{½}$ for test and reference products
    iv. Logarithmic transformed measures used for BE demonstration
    v. ANOVA for AUC_{0-t}, $AUC_{0-\infty}$, C_{max}
    vi. Inter-subject, intra-subject variability and/ or total variability if possible.
    vii. Confidence intervals for AUC_{0-t}, $AUC_{0-\infty}$, C_{max} (Confidence Interval (CI) Values should not be rounded off; therefore to pass a CI range of 80-125, the values should be at least 80.00 and not more than 125.00.
    viii. Geometric mean, arithmetic mean, ratio of means for AUC_{0-t}, $AUC_{0-\infty}$, C_{max}
    ix. Partial AUC , only if it is used
    x. C_{max}, C_{min}, C_{pd}, $AUC_{0-\tau}$, degree of fluctuation [(C_{max} - C_{min}) / C_{av}] and Swing [(C_{max} - C_{min}) / C_{min}], if steady state studies are employed.