4-1/2010-DC (Pt-Guideline)
Directorate General of Health Services
Office of Drugs Controller General (I)
Central Drugs Standard Control Organisation

FDA Bhawan, New Delhi

Dated : 10 MAR 2011

NOTICE

As you are aware that all the Requirements and Guidelines for permission to Import and/or manufacture of New Drugs for sale or to undertake clinical trials are prescribe under Schedule Y of the Drugs & Cosmetics Rules 1945. Further, Guidance for submission of Applications with respect to FDC was also uploaded on CDSCO website to further facilitate the industry for submitting the applications in a more organised manner with the required details. However, it is felt that certain issues need to be clarified to further facilitate the industry as well as all stakeholders for more clarity.

Accordingly, this office prescribes clarifications with respect to various issues as enclosed as Annexure 1. The same has also been uploaded on CDSCO website. **Comments and suggestions regarding these clarifications should be submitted within 15 days to CDSCO, FDA Bhawan, New Delhi-110002.**

(Dr. Surinder Singh)
Drugs Controller General (I)

Annexure-1

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Introduction:

Requirements and Guidelines for permission to Import and/or manufacture of New Drugs for sale or to undertake clinical trials are prescribe under Schedule Y of the Drugs & Cosmetics Rules 1945. In order to further facilitate the industry as well as all stakeholders, CDSCO hereby prescribes clarifications with respect to certain issues, details of which are as under:-

1. **Clarification with respect to Scale of Trial Batches**

Clarification:

The definition of pilot scale is already well defined in Guidance document for industry on Biological products as posted on our website i.e. www.cdsco.nic.in which is also applicable to manufacturing of New Drugs. Requirements and guidelines for permission to import and or manufacture of New Drug for sale or to undertake clinical trials are prescribed under schedule Y of Drugs & Cosmetic Rules 1945. Appendix IX of schedule Y prescribes details with respect to stability testing of New Drugs.

As per the requirements, stability testing of new drugs substances and formulations should be carried out on at least 3 primary batches at the time of submission and the batches should be manufactured to a minimum of Pilot scale.

In case of drug substances, the batches should be manufactured to a minimum of pilot scale by the same synthetic route and using a method of manufacture that simulates the final process to be used for production batches. In case of formulations, two of the three batches should be at least pilot scale and the third one may be smaller. The manufacturing process used for primary batches should simulate that to be applied to production batches and should provide products of the same quality and meeting the same specifications as that intended for marketing.

Now in order to clarify the concept/ definition of pilot scale, this office prescribe the definition of Pilot scale to facilitate the applicants for more clarity and interpretation which is in tune with the International Guidelines for submission of new drug application.

Pilot-scale batch

A batch of an API or FPP manufactured by a procedure fully representative of and simulating that to be applied to a full production-scale batch.

For example, for solid oral dosage forms, a pilot scale is generally, at a minimum, one-tenth that of a full production scale or 1, 00, 000 tablets or capsules, whichever is the larger; unless otherwise adequately justified.

However; Batch size may be kept less than 1,00,000 tablets or capsules in case of drugs indicated in Life threatening/ serious diseases or diseases of special relevance to the Indian health scenario when adequately justified.

Further, it may be clarified that for oral liquid, topical preparations and sterile preparations, pilot scale is a minimum one-tenth that of a full production scale which must be manufactured by a procedure fully representative of and simulating that to be applied to a full production-scale batch.

Note :

Simulation is to be justified with comparability data between Pilot scale and the commercial scale in respect of facility (equipment), procedure, process etc. The permission will be considered in such cases for commercial scale batches with the condition to prove consistency of commercial scale batches including in-vitro studies with a commitment of post approval stability studies of these batches.

2. Clarification with respect to significant change criteria

Clarification:

If significant change occurs at any time during 6 months testing under the accelerated storage condition, additional testing under an intermediate storage condition should be conducted and evaluated against significant change criteria.

"Significant change" for an API is defined as failure to meet its specification.

In general "significant change" for a Finished Pharmaceutical Product is defined as:

i. A 5% or more change in assay from its initial content of API(s), or failure to meet the acceptance criteria for potency when using biological or immunological procedures. (*Note*: other values may be applied, if justified, to certain products, such as multivitamins preparations.)

ii. Any degradation product exceeding its acceptance criterion.

iii. Failure to meet the acceptance criteria for appearance, physical attribute and functionality test (e.g. colour, phase separation, resuspendability, caking, hardness, dose delivery per actuation). However, some changes in physical attributes (e.g. softening of suppositories, melting of creams or partial loss of adhesion for transdermal products) may be expected under accelerated conditions, and , as appropriate for the dosage form.

iv. Failure to meet the acceptance criterion for pH, or

v. Failure to meet the acceptance criteria for dissolution for 12 dosage units.

3. Clarification with respect to mentioning of Address on Form 44

Clarification

It may be clarified that the applicant should mention the address of the actual manufacturing facility on Form 44 where simulated batches are to be manufactured.

It may further clarified that if these batches are to be used for clinical trial including BA/BE study purpose and the same must be manufactured in GMP facility.

NB: The pilot scale batches manufactured under Form-29 NOC for the purpose of examination, test or analysis for CT purpose shall only be manufactured in GMP facility.

4. Clarification with respect to submission of data for New drug by an applicant desirous to manufacture the drug under loan License in a facility of other firm who has already obtained permission from this Directorate to manufacture the same new drug in the same facility.

Clarification

- It is to be clarified that Loan licensee shall establish and submit comparability data of minimum pilot scale batch with the marketed product of the original licensee manufactured in the same facility with the same equipment to obtain Form 46 on his license.

However, if the applicant wants to manufacture new drug on P to P basis (contract agreement – manufactured by and marketed by principle), then SLA can grant such permissions.

5. Clarification with respect to Co-Packaging products

Clarification:

It is clarified that co-packaged materials may fall into any of the categories as mentioned under Guidance document to Industry for FDC and therefore requirements for submission of documents will be same as listed under the various categories.

However, it may be clarified that if the manufacturer has already Market authorization in respect of each component of co-packaged product then the quality information to support co-packaging of those pharmaceutical products will be limited to stability of the products in the co-packaging. However each pharmaceutical product should be identical in formulation and method of manufacturing to the products which have already Market Authorization.

It may further be clarified if the packaging material of the proposed comb pack is same as that of already marketed product, stability studies of the products in co-packaging may also be relaxed provided that a commitment of post approval stability studies of three consecutive batches shall be made by the applicant.

6. Clarification with respect to submission of stability data

Clarification:

It is to be clarified that as per schedule Y, an applicant is required to submit 12 months Long term stability studies and 6 months accelerated stability studies.

However, if the applicant submits both accelerated as well as real time stability data for 6 months only, then an initial expiry of 1 year may only be considered which can be concurrently increased after submission of the adequate stability data and obtaining permission from this Directorate.

Note :

Extension of shelf-life will be made on the basis of submission of Real time stability studies data.