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A Review: Generic Product Development in Pharma Industry

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ABSTRACT
The development of various pharma dosage forms similar to the innovator dosage forms needs to follow ANDA guidelines. In this review, the development of tablet dosage form is described. The guidelines, procedures strategies and stages may change or alternate according to regulatory/non-regulatory markets, industries, climatic zones etc. The pharmaceutical industry develops a product by following major stages including Literature research, Innovator's product analysis, Trail Batches for formulation optimization, Packaging Development, Manufacturing at pilot batches, Biostudies, ANDA pre-submission, ANDA submission, Process validation and re-validation for marketing lots.

Keywords: ANDA- Abbreviated New Drug Application, FDA- Food and Drug Administration, DMF-Drug Master File, API- Active Pharmaceutical Ingredient, LOD- Loss on Drying, CDER-Centre for Drug Evaluationand Research,IVIVC- In-vitro In-vivo Correlation, cGMP- current Good Manufacturing Process and SOPs- Standard Operating Procedures.

I. INTRODUCTION

To develop a quality pharma product similar to innovators called a generic product. This generic product shows as such pharmacological effect to that of the innovator's product. To develop any product in the pharma industry, the research and development department should be creative and active in their generic innovation. Product development should not infringe on the innovator's product in any instances, if the patent is infringed then the industry faces trouble solving this issue, eventhough this maylead to major loss for the industry. The generic development industry needs to follow the legally fitted framework described in this article.

2. Development of Tablet Dosage Form in Pharmaceutical Industry

A. Literature Research

To develop a quality product,one need to refer to United StatesPharmacopoeia, British Pharmacopoeia, EuropeanPharmacopoeia, Indian Pharmacopoeia, Physician Desk Reference, Martindable. Some research articles-include dissolution procedures, test methods, impurities of active moiety, new pharmacokinetic and dynamic detections. With the literature research need to do patent evaluation by following Orange Guide, FDA and CDER patent consultants (1).

B. Sourcing for Active Moiety

International suppliers that providethe same/similar moieties with the same pharmacological properties as per innovator's products need to make contact legally and confirmation about catalogues, specifications and critical data is important while sourcing active raw material(s) (2).

C. Active Moiety Evaluation

Evaluate at least two to three potential active suppliers for DMF availability (3), compliances as per USP/EP/IP/BP monographs, impurity profile and stability, physical properties and statements regarding non-patent infringements (3,4).

D. Active Moiety Purchasing and Testing

Select at least two suppliers for potential supplements of active moiety. Testing of active moiety should be conducted in research and development of the respective industry (4). Testing and cross-verification as perthe respective pharmacopoeia monographs/forum, methods based on the manufacturer, test methods and specifications according to the supplier (5).

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E. Innovator Product Purchasing and Testing

Innovator product(s) should be purchased at least 3 different lots in small and large pack size for each strength of the same product. Innovator product testing including physical parameters like tablet shape, colour, embossing, pack size, packaging material description etc. Physical testing including tablet weight, hardness, thickness, friability, % LOD etc. Innovator punch parameters also need to beevaluated in cases to avoid/solve patent infringements and legal issues. Puch details are evaluated based on tablet parameters including size, embossing, score line and shape.

Evaluation of innovator formula ingredients should be performed by analytical methods. Some microscopic observations may help to identify innovator excipients e.g. crosslinked cellulose and Avicel show specific shapes and morphologies this may be helpful for the detection of the presence of these two ingredients in the same formulation.

Evaluation of bioassay carry by reviewing FDA and CDER home page for biostudy parameters. Thedissolution profile needs to be compared with USP monographs and FDA methods for 12 units dissolution profile (6).

F. Active Moiety Analysis for Bulk Purchase

Physical characterisation analysis including particle size distribution, polymorphic form, bulk density, tapped density and microscopy etc. Chemical characterisation should be done for % assay, water content, stressed analysis, impurities testing, enantiomeric study and optical rotation (7).

G. Excipients Purchase and Testing

Excipients purchasing with their complete analysis certificate concerning particle size, Differential Scanning Calorimetry and Fourier Transform Infrared spectroscopy is necessary.

H. Container Closure System

Evaluation of suitable container-closure systems plays an important role in protecting the product during stabilities studies and ensuring that the product will be sustained at various climatic zones (8).The choice of container-closure as well as liner system depends on a material composition which may be thermoplastic resin and its pigments, manufacturer and supplier availability and access for regulatory authorities regarding DMF dossiers (9,10).

I.Manufacturing Process and Parameters

Evaluation of suitable manufacturing procedure by direct compression, granulation by both methods like wet and dry granulation then all process parameters as well as excipients ratio matters more. During the manufacturing process need to record the following parameters which are very helpful regarding product development as shown in the table.

Table: Manufacturing process and parameters

Process	Parameters
Dry granulation and slugging	Roller pressure Roller current Milling speed Drying parameters and LOD limits Determination of testing temperature for analysis of LOD without decomposing API Flow properties of the blend Particle size distribution of the blend
Wet granulation	Determination of pre-mixing blend and time Determination of binder fluid addition with impeller and chopper speed with time (granulation time) Determination of torque endpoint value Flow properties of the blend Particle size distribution of the blend
Blending & Lubrication	Time and speed of blender during blending Calculation of extra-granular material (lubricating material) Time and speed of blender during lubrication
Compression	Compression machine speed in RPM Tablet weight, thickness, hardness, friability, disintegration and dissolution
Coating	Pre-warm time for tablets, pan RPM, spray gun distance, inlet and bed temperature, coating build-up and drying time after completion of coating

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After following these processes multiple times depending on process changes, excipient changes and stability profile experiment formula gets finalised.

J. Bulk Active Moiety Purchase

Active moiety purchase for process qualification concerning pivotal batch(es). Purchase quantity depends on price, market (lot size required) and formula of the respective product.

K. Process Optimization During Process Qualification Batches

For suitable and quality product development results obtained as per R&D batch(es) process may be changed during process qualification batch(es). Changes are possible with concerning time and speed of equipment/instruments. This batch generates data for scale-up and large-scale manufacturing and results should be reproducible as like R&D inscale batch(es) and large-scale batch(es).

L. Analysis of Process Qualification Batches

Analysis should be done according to R&D analysis for dissolution in USP/desired medium and other media in comparison with the innovator's product. Should perform IVIVC study relevant to innovator's product. Establish and adjust dissolution parameters IVIVC level A and C correlation only if necessary and acceptable without adjusting dissolution parameters and time (11,12).

M. Scale-up Manufacturing

Preparation of scale-up lots if pivotal batch size problems are anticipated. Sometimes single batch is evaluated as process qualification and scale-up batch. The scale report develops the backbone for the overall product development concerning the documentation part (13).

N. Process Qualification

The process qualification includes a detailed review of the proposed formula, manufacturing processes and parameters with signatures of personnel related to production and quality assurance. Protocol of process qualification prepared and followed for key steps including critical manufacturing process designed and sampling point and parameters are specified. During manufacturing production and control personnel should be there. After completion of the Process Qualification Report, it becomes part of the development report.

O. Pivotal Batch and its Production

For the conduction of pivotal batch(es) production facilities should fulfil the minimum requirements of R&D. Pivotal batch(es) must be compressed in the same machinery that will be used for production. Batch documentation is prepared as a final master formula card. After successful completion of Regulatory Affairs personnel. A development team can decide production and control conditions if required. After the preparation of the pivotal batch data is integrated and attached to the overall product development report (12).

P. Bioequivalence study and evaluation

Biostudies were conducted for pivotal lot samples for fasted and food effects (10). Generally higher strength of a particular product is preferred for biostudy. In-case of multiple strengths product in-vitro dissolution studies conducted in different media having different pH for lower strengths only. Dissolution results are compared by similarity test (F_2 Test) (14).

Q. ANDA Pre-submission and auditing

For ANDA filing all supporting documents containing the Product Development Report need to be submitted to the FDA. The auditing plant and laboratory documentation arerequired as per ANDA (15). cGMP should be implemented in the auditing plant. Validation of SOPs related with product and machinery should be completed and signed.

R. ANDA submission

ANDA submission should be done according to FDA guidelines with 1 final copy and 9 colour copies.

S. Validation batches and process validation

Validation of process which is optimized and final, carried as a trial for 3 lots for the specified market(s) with minimum batch size required by the market. Process validation report contains data that shows similarity within 3 batches. These batches should be similar with bio-batch (pivotal) (17).

T. Commercial re-validation

Formula change can be for new processes or equipment which may have a change in operating principle.

Minor changes can be done according to SUPAC levels I II or III (18).

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