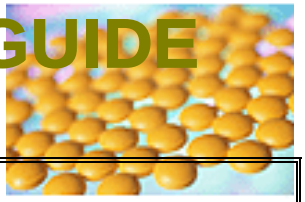
# PRODUCT DEVELOPMENT GUIDE



## PRE-FORMULATION - TABLETS

Introduction

Guidelines for the development of a ANDA product for the US market, Note: some tests or procedures may be unnecessary. The order of performing the various stages may change depending on the product under development. These guidelines may be modified for other geographic zones.

| Development Stage | Scope of Product Development |
|---|---|
| Stage 1 | Literature Search |
| Literature Research | USP BP Pharm. Eur, PDR, Martindale, Merck, Florey, Vidal |
| FDA - FOI | Summary Basis of Approval |
| On-line computerized search<br><br>FDA CDER | Electronic Data Base (articles and publication on test methods, Dissolution synthesis procedures, drug impurities, pharmacokinetics and dynamics)<br>Evaluation of Biostudy parameters, Dissolution methods. |
| Patent evaluation | Orange Guide + FDA CDER WWW Patent Consultant |
| Stage 2 | Active Sourcing |
| Sourcing for Active Raw Material | International Suppliers US, European, Asian, e.g. (ACIC-Canada) (AllChem-UK) (Lek-Czech), (Esteves; Moehs; Uquifa-Spain); (Biopharma, S.I.M, Midy-Italy) (Chemcaps, Reddy; Tricon-India); (Federa-Brussels) - Review suppliers catalogues & data critically. |
| Potential Suppliers List | Request samples and C of A and Specifications<br>Evaluate at least two suppliers fully. |
| Stage 3 | Active Evaluation |
| Evaluate Potential Actives | Evaluate at least two to three potential active suppliers<br>• DMF availability<br>• Compliance with USP monograph<br>• Impurity profile and stability<br>• Potential Polymorphic forms<br>• Commitment for physical specifications<br>• Statement of non-patent infringement |
| Stage 4 | Active Purchasing |
| Purchase (Potential) Active Material | Evaluate at least two potential active material suppliers for approved supplier status |
| Stage 5 | Active Testing |
| Testing of Active Material sample | Chemical testing by the R&D analytical lab as per<br>a. Pharmacopoeia monograph (if present)<br>b. Pharmacopoeia Forum (if available)<br>c. In-house method (based on manufacturer)<br>d. Supplier's test methods and specifications |

## PRE-FORMULATION

| Development Stage | Scope of Product Development |
|---|---|
| Stage 6 | Innovator's Product Purchasing |
| DRUG PRODUCT Innovator Samples | Purchase at least 3 different lots in smallest and largest pack size for each product strength |
| Stage 7 | Innovator's Product Testing |
| Innovator Testing | Evaluate physical parameters:- tablet shape, tablet color, code for punch embossing, pack sizes containers materials, closure types; cotton and desiccants. |
| Innovator Physical Testing | Physical testing Weight; Thickness; Hardness; LOD; Friability; Disintegration: Evaluation of tablet punch; size; score; embossing and shape |
| Evaluation of Innovator formula ingredients | Summary Formula in PDR; International PDRs (Italian, French, Swiss) and Innovators product's insert (obtain latest FOI -FDA) Perform actual analytical testing on innovator's product. |
| Microscopic observation | Particle/crystal information on Particle size Crystal shape, habit, Differentiation on the presence of specific excipients can be verified from microscopic observation. E.g., Cross-linked cellulose's Starch and Avicel have a specific shapes and morphology and maybe easily detected. |
| Evaluation of Biostudy parameters | Review FDA CDER Home page for listing and Biostudy parameters |
| Dissolution profile | USP monograph and FDA method - (where present) Dissolution; 12 unit Dissolution Profile. |
| Stage 8 | Bulk Active Testing |
| FIRST BATCH FROM APPROVED SUPPLIER Full Physical characterization | Physical characterization of bulk batch • Polymorphism • B.E.T. • Particle size distribution (& method development) • Bulk density; • Microscopic observation |
| FULL CHEMICAL CHARACTERIZATION | Chemical characterization • Assay • Stressed Analysis • Degradants (Expected) • Impurity profile • Optical rotation • Enantiomeric purity • O.V.I. Testing |

# DEVELOPMENT BATCHES

| Development Stage | Scope of Product Development |
|---|---|
| **Stage 9** | **Excipients** |
| Evaluation of formulation with suitable excipients | Excipient compatibility using DSC methods and stability assessment |
| **Stage 10** | **Container Closure System** |
| Evaluation of suitable Container-Closure System | Choice of container-closure-liner system including:<br>• material composition,<br>• type of thermoplastic resin and resin pigments,<br>• manufacturers and suppliers,<br>• liners and seals used by closure manufacturer,<br>• cotton and desiccants.<br>• manufacturer's DMF numbers for all component parts<br>• Letters of Access for regulatory authorities to view DMF dossiers |
| **Stage 11** | **Manufacturing Process** |
| EVALUATION SUITABLE MANUFACTURING PROCESSES<br><br>Wet Granulation<br><br>Dry Granulation<br><br>Slugging and Dry Granulation | • Wet granulation (aqueous or non aqueous) high shear mixing / low shear mixing<br>• FBD spray procedure), or<br>• Dry mixing, dry granulation and/'or Slugging<br>• Determination of order of mixing<br>• Determination of pre-mixing (in Granulator)<br>• Determination of fluid addition (if relevant)<br>• Determination of granulation time (chopper I & II)<br>• Determination of torque end-point value<br>• Determination of Drying parameters<br>• Determination of LOD limits<br>• Determination of testing temperature for checking LOD limits (State machine used e.g. Mettler™, Computrac™). |
| **GRANULATION** Physical Properties of Granulate | • Flow properties,<br>• Density,<br>• Particle-size distribution<br>• Compressibility |
| **Compression** Physical Properties of Compressed Tablets | • Weight, • Hardness,<br>• Thickness, • Friability<br>• Disintegration • Dissolution |
| Final Formula Established | Assessment of Final Master Formula and accelerated 1-3 month stability profile. |
| **Stage 12** | **Bulk Active Purchased** |
| Active material Bulk purchase | Ordering of Active material for Process Qualification (PQ) and Pivotal Batch(es).<br>On approval of final formula, order sufficient material for the PQ (2) and Pivotal Lots (sufficient for all strengths and batch sizes).<br>NB: Never mix batch numbers in PQ and Pivotal Lots. |

# FULL LABORATORY EVALUATION

| Development | Scope of Product Development |
|---|---|
| Stage 13 | Analytical Evaluation |
| Analytical testing of tablets/Caplets | • Dissolution - in USP medium (Multipoint profiles) and other relevant media versus Innovator's product |
| | • U of C-for low active concentrations. Refer to USP requirements for uniformity of content vs. uniformity of dosage units. |
| | • Validation of analytical package i.e. Assay; Dissolution ; Content Uniformity completed prior to Process Qualification |

## PROCESS OPTIMIZATION

| Development | Scope of Product Development |
|---|---|
| Stage 14 | Process Optimization |
| GRANULATION OPTIMIZATION | • Effect of granulation parameters |
| | • Granulation time |
| | • Speed of choppers (I & II) or mixer blades |
| | • Solvent addition rate and overall amount |
| | • Ratio of intra-granulate Disintegrant and binders agents |
| | • Screen size for milling (e.g. 0.6 or 0.8mm) |
| | • Adjusting mill screen size up or down to fine tune hardness |
| | • Evaluation of optimized granulate and tablet attributes |
| DRYING | • FB Drying temperature versus target LOD and range limits and the effect on granulate and tablet properties (flow, capping, sticking). |
| | |
| BLENDING | ◊ Blending times |
| | ◊ Lubricant Split into two parts (pre-blending and final blending) |
| | ◊ The effect on Content Uniformity, Granule lubrication and Dissolution profile. |
| | ◊ Evaluation of unit dose sampling vs. Content Uniformity |
| | |
| COMPRESSION | * Effect of hardness on tablet properties (aging, dissolution, friability). |
| | * Evaluation of Hardness Range Limits |
| | * Evaluation of stability results of optimized mfg. process |
| PROCESS OPTIMIZATION REPORT | * Prepare PO Report. This Process_Optimization Report forms part of the product Development Report |
| | |

# ESTABLISHING AND INVITRO INVIVO CORRELATION

| Development | Scope of Product Development |
|---|---|
| Stage 15 | Analytical Evaluation |
| IVIV Correlation | • Dissolution - in USP medium (Multipoint profiles) and other relevant media versus Innovator's product. |
| | • Perform IVIV Bioavailability Study (where relevant) |
| | Establish a Level A or C correlation without adjusting dissolution parameters and time scale |
| | • Adjust the dissolution parameters or time scale to achieve a Level A or C correlation (adjust only if necessary) |

## SCALE UP

| Development | Scope of Product Development |
|---|---|
| Stage 16 | SCALE UP |
| **Scale-up** | Scale-up lot prepared if larger batch size scale up problems anticipated. |
| | Process Qualification batch and Scale-up batch may be evaluated as a single batch. |
| Scale-up Report | The preparation of a Scale-up Report. The Scale-up report forms part of the overall Development Report |
| | |

## PROCESS QUALIFICATION

| Development Stage | Scope of Product Development |
|---|---|
| Stage 17 | Process Qualification |
| The process qualification batch is manufactured in order to detect any problems that may arise during the manufacture of production size batches, allowing a solution prior the manufacture of the pivotal demonstration batch. Scale-up to the pivotal batch size or 70% of the pivotal batch may be combined with qualifying the manufacturing process At this stage full manufacturing documentation is prepared alone standard procedures. | |
| PRODUCTION FACILITIES | Process Qualification batch should be compressed in a production (or production type with same principle and operation) tabletting machine |
| | Size of pivotal and marketing batch confirmed (NLT 100 000 net/ packed at *target* parameters or 10% of proposed market batch). |
| BATCH DOCUMENTATION | Preparation of Master Formula and Processing Instructions<br>Discussion of formula, manufacturing process and control parameters with production personnel and QA Staff |

## PROCESS QUALIFICATION

| Development Stage | Scope of Product Development |
|---|---|
| Stage 17 (Cont) Process Qualification | |
| FINAL REVIEW and AUTHORIZATION | Review of proposed formula, manufacturing process and control parameters with production personnel and QA Staff with authorization signatures (RD; QA-QC; RA; and Production) |
| PROTOCOL | PQ. protocol prepared |
| KEY STEPS | Critical manufacturing steps designated and sampling and testing parameters specified. |
| OPERATING CONDITIONS | Presence of production and control personnel during PQ manufacture |
| P.Q. REPORT | Upon completion prepare Process Qualification Report. This P-Q report forms part of the overall Development Report |

## PIVOTAL BATCH

| Development | Scope of Product Development |
|---|---|
| Stage 18 Pivotal Production | |
| PRODUCTION FACILITIES | Pivotal batch MUST be compressed in a production tabletting machine (or production type with same principle and operation) |
| BATCH DOCUMENTATION | Preparation of FINAL Master Formula and Processing Instructions |
| REVIEW and AUTHORIZATION | Review of FINAL formula, manufacturing process and control parameters with production personnel and QA Staff. Pivotal authorization signatures (RD; QA-QC; RA; and Production) attached. |
| OPERATING CONDITIONS | Operation of production and control personnel during Pivotal manufacture, aided by development team. |
| REPORT | The preparation of a Pivotal Report. This pivotal report forms part of the overall Development Report. |

## BIOEQUIVALENT STUDY

| Stage | Scope of Product Development |
|---|---|
| **Stage 19** | **BIOSTUDY Evaluation** |
| BIOSTUDY Fasted | Perform Fasted / Food Effect Biostudy on Pivotal Lot Samples |
| BIOSTUDY [Food Effect] | Perform Food Effect Biostudy on Pivotal Lot Samples (See food effect guidelines, where appropriate) |
| HIGHEST DOSAGE | Biostudy generally performed on highest strength of product |
| One or two studies | Fasted AND Food Effect Study may be required |
| WAIVER CONDITIONS | For multiple strength products Invitro dissolution testing conducted in three different pH media on lower dosage forms |
| SIMILARITY TESTING | Perform Similarity Test [$F_2$ Test] on dissolution results. |

# PRE-SUBMISSION AUDITING

| Development Stage | Scope of Product Development |
|---|---|
| Stage 20 | ANDA Pre-Submission Auditing |
| Development Report | Audit all raw data supporting Development Report |
| ANDA Regulatory File | Audit Plant and Laboratory Documentation as per ANDA |
| SOPs | Review SOP System and Update level |
| cGMP | Review cGMP of Manufacturing Processes |
| Biostudy Report | Evaluate and develop a IVIV correlation (Level A where possible.) |
| Validation Protocol | Product Process Validation Protocol complete and signed |

# ANDA SUBMISSION

| Development Stage | Scope of Product Development |
|---|---|
| Stage 21 | ANDA Submission |
| ANDA Submission | Submit ANDA structured as Part Two of this Handbook |
| | (9 Copies -as per Color system) |
| | (1 Field Copy) |

# VALIDATION BATCHES

| Development Stage | Scope of Product Development |
|---|---|
| Stage 22 | Process Validation |
| Protocol | Process Validation Protocol for 3 consecutive marketing lots |
| Execute validation | Process Validation of 3 consecutive marketing lots |
| Report | Process Validation Report |
| Similarity | Show intra-batch similarity |
| Bio-Validation Similarity | Show inter-batch similarity between Biobatch (Pivotal) and the Commercial Validation Lots |

# COMMERCIAL RE-VALIDATION
## DUE TO MAJOR CHANGE

| Development Stage | Scope of Product Development |
|---|---|
| Stage 23 | Process Re-validation |
| Formula Change | Revalidate procedure with new formula process or equipment with |
| Process Change | a different operating principle |
| Equipment Change | |
| Minor change | Follow SUPAC Rules Level I II or III |
| | |

## IMPORTANT NOTE ON DEVELOPMENT

**D**evelopers are encouraged to develop IVIVC for IR dosage forms, where applicable to the BCS, (Biopharmaceutical Classification System) in the expectation that the information will be useful in establishing appropriate dissolution specifications and thus permit certain post approval formulation and manufacturing changes to be effected, - without additional bioequivalence studies.

**T**he objective of developing an IVIVC is to establish a predictive mathematical model describing the relationship between invitro dissolution settings and the actual invivo drug-plasma parameters found, (such as AUC, $C_{max}$, $T_{max}$).

**T**he invitro dissolution settings are adjusted (via media, pH agitation) until a I : I correlation is achieved (Level A) or a single dissolution point and a plasma parameter is shown to correlate (Level C).
When more than one point correlates a multiple Level C is obtained - which may possibly be upgraded to a Level A with additional development work.

**T**his matching of dissolution settings with plasma levels, that are derived from a specific IR formula and its corresponding manufacturing process, is in fact simply an arbitrary set of values that establish the so called 'predictive mathematical model'.

**A**n IVIVC should be evaluated to demonstrate that predictability of the invivo performance of the drug product (i.e. derived from the plasma parameters) from its in vitro dissolution characteristics (e.g. equipment settings / and manufacturing changes) is maintained over the product's dissolution profile