PRODUCT DEVELOPMENT GUIDE

CONTROLLED RELEASE DOSAGE FORMS

PRE-FORMULATION

Introduction

Guidelines for the development of a controlled release product primary for the US market, Note: some tests or procedures may be unnecessary for certain products. 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	Scope of Product Development Stage
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 FDA CDER	Electronic Data Base (articles and publication on test methods, Dissolution synthesis procedures, drug impurities, pharmacokinetics and dynamics) 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. Lek (Czech) ZIP, Esteves, (Spain); (Mohrs Spain) (S.I.M Italy) Review Suppliers Catalogues
Potential Suppliers List	Request samples and C of A and Specifications Evaluate at least two suppliers fully.
Stage 3	**Active Evaluation**
Evaluate Potential Actives	Evaluate at least two to three potential active suppliers • DMF availability • Compliance with USP monograph • Impurity profile and stability • Potential Polymorphic / solvate forms • Commitment for physical specifications • 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 a. Pharmacopoeia monograph (if present) b. Pharmacopoeia Forum (if available) c. In-house method (based on manufacturer) d. Supplier's test methods and specifications

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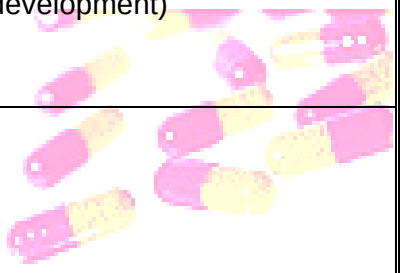
FORMULATION

Development	Scope of Product Development Stage
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
Evaluation of Biostudy parameters	Review FDA CDER Home page for listing and Biostudy parameters Developing a meaningful IVIVC on a product -by-product-basis
Dissolution profile IVIV Correlation	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	Choice of Releasing and Non-releasing controlling excipients Evaluating predictability models. Excipient compatibility using DSC methods and stability assessment Choosing dissolution parameters (sampling times and percentage dissolved ranges) Determining several dissolution profiles during formulation; optimization; final formula & process qualification
Stage 10	**Container Closure System**
Evaluation of suitable Container-Closure System	Choice of container-closure-liner system including: • material composition, • type of thermoplastic resin and resin pigments, • manufacturers and suppliers, • liners and seals used by closure manufacturer, • cotton and desiccants. • manufacturer's DMF numbers for all component parts • Letters of Access for regulatory authorities to view DMF dossiers
Stage 11	**Manufacturing Process**
EVALUATION SUITABLE MANUFACTURING PROCESSES Wet Granulation Dry Granulation Slugging and Dry Granulation	• Wet granulation (aqueous or non aqueous) high shear mixing / low shear mixing • FBD spray procedure), or • Dry mixing, dry granulation and/'or Slugging • Determination of order of mixing • Determination of pre-mixing (in Granulator) • Determination of fluid addition (spray rates, if relevant) • Determination of granulation time (chopper I & II) • Determination of torque end-point value • Determination of Drying parameters • Determination of LOD limits • Determination of testing temperature for checking LOD limits (State machine used e.g. Mettler™, Computrac™).
GRANULATION Physical Properties of Granulate	• Flow properties • Density, (bulk; tapped) • Particle-size distribution • Compressibility (Carr's Compression index)
Compression Physical Properties of Compressed Tablets	• Weight, • Hardness, • Thickness, • Friability • Disintegration • Dissolution
Final Formula Established	Assessment of Final Master Formula and accelerated 1-3 month stability profile

ACTIVE PURCHASE

Stage 12	Bulk Active Purchased
Active material Bulk purchase	Ordering of Active material for Process Qualification (PQ) and Pivotal Batch(es). On approval of final formula, order sufficient material for the PQ (2) and Pivotal Lots (sufficient for all strengths and batch sizes). NB: Never active mix batch numbers in PQ & 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.
Dissolution Validation	• Validation Of Dissolution Method; With Choice Of All Discriminatory Dissolution Parameters (Usp Type; Media; Ph; Agitation) Completed Prior To Process Optimization And Process Qualification NOTE: Dissolution parameters (as above) may well be adjusted to establish a Level A or C correlation after IVIV study
Validation Package	• 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) ◊ Evaluation of optimized granulate and tablet attributes
DRYING BLENDING COMPRESSION	♦ FB Drying temperature vs. target LOD and range limits. Effect on granulate and tablet properties (re: flow, capping, sticking). ♦ 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. ♦ Effect of hardness on tablet - 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. Dissolution Report included.

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DISSOLUTION PROFILING

Development	Scope of Product Development
Stage 15	**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

ESTABLISHING AND INVITRO INVIVO CORRELATION

Development	Scope of Product Development
Stage 16	**Analytical Evaluation**
IVIV Correlation	• Dissolution - in USP medium (Multipoint profiles) and other relevant media versus Innovator's product. • Perform IVIV Bioavailability Study
	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 Stage	Scope of Product Development
Stage 17	**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 18	**Process Qualification (PQ)**
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.	

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PROCESS QUALIFICATION

Development Stage	Scope of Product Development
Stage 18	**Process Qualification - (Continued)**
PRODUCTION FACILITIES	Process Qualification batch should be compressed in a production (production type with same principle & operation) tabletting machine
BATCH SIZE	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 Discussion of formula, manufacturing process and control parameters with production personnel and QA Staff
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; sampling and testing parameters specified.
OPERATING CONDITIONS	Presence of production and control personnel during PQ manufacture
DISSOLUTION PROFILE	12 POINT DISSOLUTION profile of PQ batch.
PROCESS QUALIFICATION REPORT	Upon completion prepare P-Q Report. This P-Q report forms part of the overall Development Report

PIVOTAL BATCH

Development	Scope of Product Development
Stage 19	**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.
	The preparation of a Pivotal Report. This pivotal report forms part of the overall Development Report.

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BIOEQUIVALENT STUDY

Stage	Scope of Product Development
Stage 20	**BIOSTUDY Evaluation**
BIOSTUDY	Perform Food Effect AND Fasted Biostudy on Pivotal Lot Samples
HIGHEST DOSAGE	Biostudy generally performed on highest strength of product
TWO STUDIES	Food Effect AND Fasted Study required for CR/MR/ER forms
WAIVER CONDITIONS	For multiple strength CR 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

Stage	Scope of Product Development
Stage 21	**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
Validation Protocol	Product Process Validation Protocol complete and signed
Biostudy Report	Evaluate and develop a IVIV correlation (Level **A** where possible)

ANDA SUBMISSION

Stage	Scope of Product Development
Stage 22	**ANDA Submission**
ANDA Submission	Submit ANDA after thorough in-house audit review
	Biostudy Section 6 (Separate File)
	(9 Copies - as per Color system)
	(1 Field Copy)

VALIDATION BATCHES

Stage	Scope of Product Development
Stage 23	**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

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COMMERCIAL RE-VALIDATION DUE TO MAJOR CHANGE

Stage	Scope of Product Development
Stage 24	**Process Re-validation**
Formula Change	Revalidate procedure with new formula process or equipment with
Process Change	a different operating principle
Equipment Change	Follow SUPAC **MR** Rules Level I, II or III
Minor change	Follow SUPAC **MR** Rules Level I

IMPORTANT NOTE ON DEVELOPMENT

Developers are encouraged to develop IVIVC for CR/ER dosage forms in the expectation that the information will be useful in establishing dissolution specifications and will permit certain post approval formulation and manufacturing changes without additional bioequivalence studies.
The 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, (AUC, C_{max}, T_{max}).

The 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 work.
This matching of dissolution settings with plasma levels, that are derived from a specific CR formula and its corresponding manufacturing process, is in fact simply an arbitrary set of values that establish the so called 'predictive mathematical model'.

An IVIVC should be evaluated to demonstrate that predictability of the invivo performance of the drug product (plasma parameters) from its in vitro dissolution characteristics (equipment settings) is maintained over a range of dissolution release rates and manufacturing changes.

DEFINITIONS.

MR Modified Release Solid Oral Dosage Forms include both delayed and extended release drug products

ER Extended Release Dosage Form: A dosage form that allows a *reduction* in dosage frequency as compared to that presented by conventional dosage forms such as a solution or an immediate release dosage form

DR Delayed Release The release of a drug at a time other than immediately following oral administration

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STANDARD OPERATING PROCEDURES

SOP # HPGD-02-Y2K

CR FORMULA DEVELOPMENT

The following selected model Standard Operating Procedures are recommended for a controlled release development unit:

DEVELOPMENT SOPs

HPGD-02-Y2K Setting up a *Product Specific* **ER** Development SOP.

HPGD-02-Y2K Setting up IVIVC for **E**xtended **R**elease *Oral Dosage Forms*

HPGD-02-Y2K Contents of a Development SOP - **ER** Oral Tablets.

DEVELOPMENT FORMULA

HPGD-02-Y2K Formulation of CR / ER[1] ANDA Oral Tablet Preparations

HPGD-02-Y2K Establishing an IVIVC in Extended Release *Oral Dosage Forms*

HPGD-02-Y2K Standard Procedures for Generic Product Development

HPGD-02-Y2K Establishing a level A IN-VITRO IN-VIVO correlation

HPGD-02-Y2K Establishing a level B IN-VITRO IN-VIVO correlation

HPGD-02-Y2K Establishing a *standard* level C IN-VITRO IN-VIVO correlation

HPGD-02-Y2K Establishing a *multiple* level C IN-VITRO IN-VIVO correlation

DEVELOPMENT REPORT

HPGD-02-Y2K Evaluating the predictability of a level A - IVIV Correlation

HPGD-02-Y2K Development and Evaluating of a level C IVIV Correlation

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