PRODUCT DEVELOPMENT GUIDE

PRE-FORMULATION - SOFT GELATIN CAPSULES

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, Text and journals
FDA - FOI	Summary Basis of Approval - On request form FDA
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. (ACIC-Canada) (AllChem-UK) (Lek-Czech), (Esteves; Moehs; Uquifa-Spain); (Biopharma, S.I.M, Midy-Italy) (Chemcaps, Reddy; Tricon-India); (Federa-Brussels) - Review suppliers catalogs & data critically.
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 or maximum three potential active suppliers • DMF availability • Compliance with USP monograph • Impurity profile and stability • Potential Polymorphic forms • Commitment for physical specifications (Bulk Density) • 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 specification

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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:- Capsule size, capsule color / US approved dyes, coding for printing, pack sizes containers materials, closure types; cotton and desiccants, blister packaging.
Innovator Physical Testing	Physical testing Fill Weight & Uniformity; Shell disintegration & Dissolution Evaluation of capsule size and volume w.r.t. fill volume
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, rugosity Viscosity agents used (PVP 30 / 90) Presence of vegetable oil (type) Presence of PEG 400 Presence of polyethylene glycol solvent
Evaluation of Biostudy	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 and Tapped density (Need for size reduction of material) • Microscopic observation
FULL CHEMICAL CHARACTERIZATION	Chemical characterization • Assay • Stressed Analysis • Degradants (Expected) • Impurity profile • Optical rotation • Enantiomeric purity • O.V.I. Testing

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DEVELOPMENT BATCHES - SOFT GELATIN CAPSULES

Development Stage	Scope of Product Development
Stage 9	**Excipients**
Evaluate formulation with suitable excipients	• Vegetable oil solubility / PEG 400 / PEG 600 / PG / PVP 30 • Antioxidants (dl-alpha Tocopherol (Vit. E USP) / Propyl gallate)
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 Gelatin Mass Fill Preparation Encapsulation Drying stages	• Gel mass blending (rpm & time) • Gel mass melting (temperature and vacuum) • Gel mass color addition (temperature and rpm & time) • Gel mass VISCOSITY and MOISTURE determination • Gel mass deaeration (holding time) • Fill mass (mixing rpm, time & propeller position) • Determination of Fill mass viscosity / SG / moisture • Determination of Bulk Uniformity Analysis • Wet shell weight / Fill weight • Seal thickness • Determination of Drying Parameters • Determination of rotary tumbler drying parameters & time • Determination of primary and secondary tray drying times • Determine Bareiss hardness
Fill material Physical Properties of oil or paste fill	• Viscosity - (Critical) • Fill moisture • SG (helps to control deaeration)
Filling Physical Properties of Filled Softgels	• Weight Uniformity (7.5%) • Individual Fill Weight Limits • Content Uniformity (5.0%) • Average Fill Weight Limits • Disintegration • Dissolution profile
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). On approval of final formula, order sufficient material for the PQ (2) and Pivotal Lots (sufficient for all strengths and batch sizes). NB: Never mix batch numbers in PQ and Pivotal Lots.

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FULL LABORATORY EVALUATION - SOFTGELS

Development	Scope of Product Development
Stage 13	**Analytical Evaluation**
Analytical testing of Softgels 	• Dissolution - in USP medium (Multipoint profiles) and other relevant media versus Innovator's product. Dissolution testing may not be possible where active strength is in micrograms (i.e. 0.25 or 0.5 mcg) • 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**
GEL & FILL MATERIAL OPTIMIZATION [In suspension and paste fills size reduction of active material may be necessary i.e. to decrease active bulk densities from 0.6 -0.75g/cc to 0.35 - 0.45 g/cc]	◊ Optimization of gel mass moisture (once per shell formula) ◊ Optimization of gel mass viscosity (once per shell formula) ◊ Deaeration of gel mass - (critical) ◊ Optimization of antioxidant percentage. ◊ Mixing process - rpm ; mixing time ; propeller position ◊ Fill material uniformity ◊ Ribbon Thickness adjustments for correct shell weights (once per shell formula) ◊ Seal Thickness (once per shell formula NLT 0.006")[1] ◊ Wet Shell Weight variation (± 8%)[1] ◊ Fill Weight variation (± 2%)[1] ◊ [1] Process capability performed.
DRYING	♦ Drying time temperature versus shell moisture (in rotary dryer) ♦ Primary drying time versus shell moisture (in tray dryer) ♦ Secondary drying time versus shell moisture (in tray dryer) ♦ Bareiss hardness versus drying times. ♦ Softgel properties (Fill weights and Content Uniformity). ♦ Evaluation of Fill weight Range Limits (Qualification) ♦ Evaluation of stability results of optimized mfg. Process. ♦ Printing Inspection Limits
PROCESS OPTIMIZATION REPORT (PO)	Prepare PO Report. This Process Optimization Report forms part of the product Development Report

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ESTABLISHING AND INVITRO INVIVO CORRELATION

Development	Scope of Product Development
Stage 15	**Analytical Evaluation**
IVIV Correlation (search literature)	• Dissolution - in USP medium (Multipoint profiles) and other relevant media versus Innovator's product. Dissolution testing may not be possible where active strength is in micrograms (i.e. 0.25 or 0.5 mcg) • Perform IVIV Bioavailability Study (where relevant)
BSC System IVIVC 1 : 1 Correlation Dissolution settings Plasma parameters	Developers 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. 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, (such as AUC, Cmax, Tmax). 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 development work. This 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'. An 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.
Not applicable to highly soluble materials	Establish a Level A or C correlation without adjusting dissolution parameters and time scale.
Not applicable to highly soluble materials	• Adjust the dissolution parameters or time scale to achieve a Level A or C correlation (adjust only if necessary)

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SCALE UP

Development Stage	Scope of Product Development
Stage16	**Scale-up**
Scale-up	Scale-up lot prepared if larger batch size scale up problems anticipated.
	Scale-up of gel mass Scale-up of fill material (N_2 atmosphere and final filtration) Scale-up of encapsulation procedure (seal thickness) Scale-up of primary and secondary drying (Time & moisture) Scale-up of sorting, sizing and printing.
	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 executed on a commercial production (or production type with same principle and operation) encapsulating machine in a production setting. The primary dryer and secondary tray or tunnel drying equipment should be identical or similar.
	Size of pivotal and marketing batch confirmed (NLT 100 000 net/ packed at *target* parameters or 10% of proposed market batch). Ideally for Soft Gelatin Capsules 120 000 - 150 000 or more units should be prepared for pivotal batch to allow for some level of qualification by testing and challenging both ends of the selected specification limits.
BATCH DOCUMENTATION	Preparation of Master Formula and Processing Instructions Discussion of formula, manufacturing process and control parameters with production personnel and QA Staff

PROCESS QUALIFICATION - SOFTGELS

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
PQ 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 Encapsulating 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.

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PRE-SUBMISSION AUDITING - SOFTGELS

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 - SOFTGELS

Development Stage	Scope of Product Development
Stage 21	**ANDA Submission**
ANDA Submission	Submit ANDA structured carefully as per Feb. 1999 Guidelines
	(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