U.S. Regulations for Flexible Pharmaceutical Packaging Materials

Mr. R.M. Gupta (M. Pharm.), is a free lance consultant for US DMF, COS, ANDA, ACTD, CTD, eCTD and other regulatory submissions. guptarmg1952@gmail.com

He is associated with Perfect Pharmaceutical Consultants Pvt. Limited and Global Institute of Regulatory affairs (Pune, India). He is dedicated solely to regulatory profession. This article is solely written to guide, educate and train regulatory community at large.

This article is based self experience of 25 years of the author in serving Flexible packaging Industry for meeting their US DMF Type III Registrations and Facility Audit

Summary:

The flexible packaging materials are largely used in Pharmaceuticals for blister packaging of tablets and sachet packing of dispersible powders. Almost 75 % of oral tablets and powders are packaged in US are packaged in flexible materials.

US 21 CFR and USP 34 NF 29 have prescribed a set of specification for controlling the quality of such materials.

US FDA also offers registration of Flexible packaging materials under US DMG Type III.
A very large number of Indian Companies have upgraded their site to meet US FDA requirements and have applied for US DMF. This article is written to guide Flexible Packaging material manufacturers/exporters/processors to know current US FDA requirements and to upgrade their facilities accordingly

The author has person experience for filing US DMF Type III for Packaging materials for large number companies including HINDALCO**.**

Introduction:

Flexible Packaging in context to Pharmaceuticals is non-rigid packaging structures used to package and protect various drug products such as tablets, capsules, powders for medical use.
Flexible packaging covers materials that have undergone a conversion process including printing, lamination, coating and extrusion, and can involve different substrates such as plastic films, paper and foil. Flexible pack types include plastic bags, wrapping films, lidding films, aluminum foil laminates; foil lidding, blister packaging, foil bags and sachets.

Flexible packaging films can be made from:

* Single materials such as PE, PP, polyester or PU
* Multiple materials by coating, laminating or co extruding with the other materials

The most common forms of flexible packaging are the strip package, blister package and the pouch.

A blister package usually consists of a lidding material and a forming film.
The lidding material is usually a laminate which includes a barrier layer (e.g., aluminum foil) with a print primer on one side and a sealing agent (e.g., a heat-sealing lacquer) on the other side.

The pouch is usually sealed from 3 sides and one side is kept open for filling and sealing thereafter. The sealing agent contacts the dosage form and the forming film. The forming film may be a single film, a coated film, or a laminate. Leak testing is usually performed on flexible packages as part of the in-process controls

According to one estimates, more than two-thirds of all medicines are delivered orally and are therefore likely to be packed in blisters/pouches/strips/bags
The most common examples of flexible Pharmaceutical packaging materials are: Aluminum Foil, **BOPP (**biaxial oriented polypropylene), **LDPE (**low-density polyethylene) **LLDPE (**linear low-density polyethylene) **OPP** (oriented polypropylene) **PA (**polyamide) **PE** (polyethylene) **PET** (poly ethylene terephthalate), **PP (**polypropylene), **PVC** (poly vinyl chloride) PVDC **(**polyvinylidene chloride), as used singly or in laminate form.

A. The basic requirements for flexible Packaging materials as per US FDA

The product shall be manufactured as per cGMP Guidelines provided under directive 21 CFR parts 11. The products used for as primary packaging of pharmaceutical products shall be manufactured under clean room conditions meeting Class 1, 00,000 cleanliness standards**.**

1. The container shall meet all requirements under 21 CFR Direct Food Contact and physical tests in accordance to latest USP <661>:

2. The container shall protect the contents from environmental hazard and external influences (e.g. moisture, light, oxygen and temperature variations) during its entire life time beginning from packaging, transportation, handling and storage until use.

3. It shall not be composed, in whole or in part, of any poisonous or deleterious substance which may render the contents injurious to health

4. It shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug beyond the official or established requirements.

5. The integrity of the flexible material must be met throughout the whole of the intended shelf-life of the product. The materials shall be conditioned to the 23°C and 50% RH before conducting any QC/QA tests.

6. Recycled starting material or finished product is mostly not allowed.

7. The product shall be supported by Certificate of Analysis (COA) or Certificate of Certification (COC) from the component supplier and the performance of an appropriate identification test, provided the supplier's test data are periodically validated (21 CFR 211.84(d)(3)).

8. All test methods shall be fully described.

9. If a batch is to be accepted based on a supplier's COA or COC, then the procedure for supplier validation should be described. The data from the supplier's COA or COC should clearly indicate that the lot meets the applicant's acceptance criteria.

10. Dimensional information shall be provided via a detailed schematic drawing complete with target dimensions and tolerances

11. Description of the quality control measures used to maintain consistency in the physical and chemical characteristics of the material.

12. A complete description of the process and its validation should be provided.

B. Characterization of flexible Materials as per USP and US Drug laws:

The flexible packaging materials are usually characterized as per below:

Material specification, IR spectrums & DSC thermo grams of standard & sample
Manufacturer's test report (COA) ,Dimensional drawing ,DMF authorization letter from manufacturers of resins and colorants ,Thermal analysis ,Light transmission ,Non-volatile residue ,Heavy metals ,Container permeation

The following physical tests are performed in accordance to latest USP <661>:
Multiple internal reflectance's (to ensure that the material of the container falls within the range of HDPE or LDPE as specified in the test) ,**Thermal analysis (to check compliance to pre defined** endotherms and exotherms temperatures) , **Light transmission (** to check protection from light) ,**Water vapor permeation (** to check protection from moisture permeation) **Heavy metals , Nonvolatile residue.**

Followings are the requirement of Flexible Packaging material as per US FDA standards.
Please note that all the tests are not required to be performed routinely.
The routine tests are marked with *
The tests required at regular intervals (3 to 6 months) are marked with ***

No	Requirements	Purpose
1	Material Name, product code, brief description, Materials of construction and the address of the manufacturing site shall be provided	Material and site identification
2	Test Reports on Polymeric materials and auxiliary substances used in manufacturing flexible laminates/.	To ensure suitability of each material**(Suppliers Test report acceptable)**
3	Description of the manufacturing process and operations A description of the quality control measures Description of the acceptance, in-process, and release controls	To assess chemistry manufacturing and Control Procedures
4	Engineering Drawing	To ensure length, width, thickness and arrangements of different polymeric layers in laminated material
5	Identification of individual Polymer Film by IR spectrophotometer	To confirm the claimed identity of Polymer monitor consistency in composition
6	Identification of each layer of the laminate by combination of FTIR and Microscopy	To confirm the claimed composition of the laminate
7	Identification of pigments and colorant such as Titanium dioxide by IR	To confirm claim identity of colorant used
8	Identification of solvents retained after printing and lamination by G.C.	To confirm that the product is free from solvents
9	Sealability : It is determined by heat sealing the product at varying temperatures; dwell time and seal pressure	To ensure protection from moisture, air, dust and microbial flora
10	Melt flow Rate; It is a measure of the viscosity of a molten polymer.	It is useful for fixing processabilty of the polymer

11	Migration test/Extraction Test: Strips are cut from the packs and immersed for 24 hours in Hexane at 50C, Ethanol at 70C Water at 70C. The non volatile residue, the pH and heavy metal content of the aqueous extract are measured. These studies may be performed on routine basis also. The term migration refers to the transfer of non volatiles compounds between a pack, the product or the environment. One method is the use of FT-IR microscopy, where a migrant's migration is tracked by monitoring a particular wavelength due to the migrant through the thickness of the polymer.	To control n water and organic solvent extractable substances.
12	Appearance of solution *(Water Extract) USP 34 <661>:	To check content of any deleterious substance which may render the contents injurious to health
13	Acidity or alkalinity *(Water Extract) USP 34 <661>:	To check content acidic/alkaline additives
14	UV absorbance (220–340 nm) *(Water Extract) USP 34 <661>:	To check content of any deleterious substance which may affect the pH of the product resulting in adverse effect on the safety of the contents
15	Reducing substances *(Water Extract) USP 34 <661>:	To check content of any deleterious substance which may render the contents injurious to health
16	Sulphated ash *(Water Extract) USP 34 <661>:	To check content of metallic residues which are known to be injurious to health
17	Substances soluble in hexane *(Water Extract) USP 34 <661>:	To check content of any deleterious substance which may render the contents injurious to health
18	Nonvolatile residue *(Water Extract) USP 34 <661>:	To check content of any deleterious substance which may render the contents

		injurious to health
19	Residue on ignition *(Water Extract) USP 34 <661>:	To check content of any deleterious substance which may render the contents injurious to health
20	Heavy metals *(Water Extract) USP 34 <661>:	To check content of undue toxic metals which are known to be injurious to health
21	Buffering capacity *(Water Extract) USP 34 <661>:	To check content of any deleterious substance which may render the contents injurious to health
22	Tensile strength/ Packaged Length, weight Lenth,width,thickness/Appearance/Total weight with Core/Nett Weight/Date of Mfg/Lot No	
23	Impact resistance	To ensure product integrity against impacts during manufacturing, packaging, shipping and storage of the product
24	Thermal analysis	To measure changes of the properties of materials as they are heated or cooled normally.
25	Differential Scanning Calorimetric	To differentiate between single polymer, homo and copolymers and polymer blends and multilayer laminates. To determine the thermal stability and effectiveness of antioxidants of polymers To measure the degree of oxidation occurring during the manufacturing cycle
26	Thermal Mechanical Analysis .	To derive orientation of polymeric molecules into packaging films to improve

		their barrier properties. It can also predict the maximum operating temperature of a polymer. It can also compare the softening temperatures of heat-seal lacquers applied on polymers
27	Size exclusion chromatography is a means of determining the molecular weight distributions of polymers by liquid chromatography	It is useful to check migration of additives
28	Water vapor permeation: Fill the container with calcium chloride and weigh. Expose the container to high humidity and temperature. Weight he container at regular intervals. The test also takes at least 14 days.	It is useful for measure water permeability of the film. This property is useful when the product is moisture sensitive.
29	Oxygen transmission Rates: Oxygen transmission rates are tested using specific instruments. Oxygen is passed over one side and nitrogen over the other side of a film held in a sealed cell. The nitrogen and the oxygen permeating through the film are passed through a coulometric cell whose current output is proportional to the oxygen transmission rate. The permeation rates are dependent on temperature and the concentration differences of the permeate either side of the barrier.	To ensure protection of the product against oxygen permeation
30	Light: For products that are sensitive to light – mainly ultra violet, the packaging must be able to provide a suitable barrier. To measure the light transmission of transparent materials a UV spectrophotometer operated in a conventional mode may be used. But for pigmented plastics where light scattering of the light by the pigment particles occurs, then the spectrophotometer must be equipped with an Integrating sphere.	To ensure protection of the product t against light radiation
31	Environmental stress crack test: The test pieces are notched, flexed and put into contact with the test product. A note is made of propagation of cracks from the notch and the results recorded graphically.	To ensure integrity under stress conditions such as transportation, handling, fall, jerks
32	Shelf Life : The product is stored at ambient temperature and humidity for 12 to 36 months	To check integrity of material throughout its intended shelf life

C. The tests generally required during production of flexible material. In many case they may also be also be used for final quality control of the product.

No	Test	Instrument Required
1	Tensile Strength	Auto Tensile Tester
2	Abrasion resistance For printed materials like labels	Ink Rub Tester
3	Impact Resistance	Drop Dart Impact Tester
4	Specific Gravity	Densimeters
5	Coefficient of static and kinetic friction of plastic films Peel strength test of adhesive laminated products.	Friction/Peel Tester
6	Film Thickness	On-line non-contact and non-destructive X-ray measurement of film thickness
7	Hot seal parameters of laminated films	Hot Tack Heat Seal Tester
8	Tear Test (To determine the average force required to propagate a single-rip tongue-type tear starting from a cut.	Tear Tester
9	Film Thickness	Film Thickness Gauges
10	Leak and Seal Strength / burst pressure Test	Leakage tester
11	Leak proofing /Seal Proofing and bursting pressure strength	Leak / Seal Strength Detector
12	Free Shrink Test	Free shrink tester
13	Gas, oxygen and water vapor Film Permeation Test	Film Permeability Testers
14	Package Drop Test	Package Drop Tester
15	Relative opacity.	Opacity Meter
16	Puncture Test (This tester measures the energy required to puncture plastic)	Puncture Tester
17	Automatic Bursting Strength Test	Automatic Bursting Strength Tester
18	Tensile , compression, flexure , shear, peel, fatigue cycling, Test	Tensile Tester
19	Box Compression	Box Compression Tester
20	Haze-Guard Test	Haze guard tester
21	Gloss Index	Gloss Meters
22	Minimum Film Formation Temperature	Minimum Film Formation Temperature Tester

D. Other Requirements for Manufacturing Flexible Packaging products:

No	Function	Purpose
1	Workers should be protected from the possibility of skin or eye contact with molten polymer. Workers shall wear Safety glasses to prevent mechanical or thermal injury to the eyes.	Workers safety
2	Molten polymer produces an unpleasant odor when contact in air. In higher concentrations the odor of molten product may cause irritation of the mucus membranes	Workers safety
3	An effective air handling system shall be provided in molding/extrusion areas to carry away fumes or vapors of polymeric materials and solvents used in processing. The area shall be well ventilated	Workers safety
4	The strict compliance to GMP shall be adhered at work place.	Workers safety
5	Most of the resins are inflammable when heated. Avoid excessive heating. The store away from direct flame and ignition sources. Store in cool ventilated place.	Workers safety
6	Most of the resins contribute thick black smoke on burning. Suitable hydrant system shall be in place for extinguishing primary fire. In addition advance fire extinguishing system based on heavy foams forming system shall be available	Workers safety
7	The material shall be Rolled up tightly and evenly The sides shall be neat and even.	Packaging and storage
8	The inner core shall not be loose broken and concave. The joint per roll shall not be more than 2. The material shall be protected with sufficiently durable plastic material covering and sealing all sides	Packaging and storage
9	Store the material under ambient conditions. Avoid storage at temperature above 40 C. Avoid storage near UV radiation. Protect from direct sunlight. Protect from high atmospheric humidity. The materials stored unintentionally at higher temperature or humidity due to any constraints shall be consumed on priority.	Packaging and storage

Conclusion: Flexible Packaging Materials for Pharmaceutical packaging's are strictly controlled by various US FDA regulations. The entire development storage, manufacturing, controls, validation and distribution of the finished products shall be performed under Good manufacturing Practices.

Disclaimer: The article does not cover flexible materials used for bulk packaging. It does not cover rigid plastic bottles and containers

Note: The article cover total guidelines provided under USP and 21 CFR and voluntary tests which can be performed in support to the US FDA requirements.

References:

- Code for good manufacturing practices of flexible and fiber-based packaging for food, *www.flexpack-europe.org, July 2011.*

- Guidance for industry, container closure systems for packaging ,Human drugs and biologics, chemistry, manufacturing, and controls documentation , http://www.fda.gov/cber/guidelines.htm

- Tom Dunn,US FDA Regulations for Plastics in Food Packaging, http://flexpacknology.com/uploads/2/8/4/0/2840779/us_fda_regulation_of_plastics_used_in_food.pdf

- USP 34 and NF 29 , Chapter <661>, Plastic Containers

- US FDA Regulations : 21 CFR 211.132, 21 CFR 211.80(b), 21 CFR 211.42(b), 21 CFR 211.132, 21 CFR 211.80(b) ,21 CFR 211.94 a), 21 CFR 175.300

  Vishwas Pethe, Mike Dove, Alex Terentiev, Integrity Testing of Flexible Containers - Defects as small as 10 μm can be detected without compromising product cleanliness using helium integrity testing , Biopharma International ,Volume 24, Issue 11, pp. 42-49 , Nov 2, 2011 (biopharminternational.findpharma.com)

- Magali Barbaroux, Andrew Sette Properties of Materials Used in Single-Use Flexible Containers: Requirements and Analysis - Properties of Materials Used in Single-Use Flexible Containers: Requirements and Analysis, Biopharma International ,Nov 2, undefined Sep 26, 2007, (biopharminternational.findpharma.com)