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Mini Review

Pharmacovigilance and Role of Packaging

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Abstract

Packaging plays an essential information medium through labelling and package insert(leaflet) for pharmacovigilance. Pharmacovigilance team is collecting data, identify the actual problem, assessment, monitoring and prevention of adverse effect of the Pharmaceutical products. It may happen due to wrong design of Primary Packaging device and material as well. Wrong Medication guidance like overdose and misuse and abuse of a drug as well as drug exposure during pregnancy and breastfeeding, are also of interest, even without an adverse event, because they may result in an adverse drug reaction.

Licence holder drug manufacturing company need to take immediate action once they receive and complaint from patients or from any hospitals. This information can be transmitted through SMS, Facebook, E-mail ,phone call or report to the Pharmacovigilance team.

Keywords: Pharmacovigilance; Packaging

Purpose and special role

- Before using any drugs Patients, Pharmacists, nurses and others are going through the instruction in container label and package insert those are made my experienced Packaging Technologist**.**
- Any special information pass to the Patient related to drug delivery need to verified by medical officer and marketing Authorization is a must.
- Selection of primary packaging material is most important to avoid product stability loss before shelf life.
- Package insert is most important since when any Physician and Nurses are not available around.
- User friendly Packaging also guarantees the good use of medicine products and promotes Patient Compliance (i.e. calendar) [1-4].

Adverse reaction of drugs can possible related to Packaging for below reasons:

1. Extractable and leachable from Glass Vial, Syringe and cartridge, rubber stopper and plunger.
2. Silica flex floats into the product due to Delamination of Glass
3. Extractable and leachable from "Polymeric Vial, syringe and cartridge.
4. Primary packaging material is not compatible with ophthalmic product.
5. Contamination of inhaler product due to "Extractable and Leachable"
6. IV Infusion contaminated due to extractables from Tube.
7. Wrong selection of Polymer in "Nitrocellulose patch.
8. Wrong design of "Autoinjector"
9. Tablet/capsule colour change in blister pack due to Extractables from Primary Packaging Material.
10. Wrong instructions in Package insert

Figure 1

Figure 2

Extractable and leachable from Glass Vial, Syringe and cartridge, rubber stopper and plunger.

Type of Packaging Materials	Reason for adverse reaction and solution
	Problems Extractable and Leachable Alkali Oxides Trace Metals Delamination of glass **Interactions with Drug Products - Biologics** Particulates pH Shifts Protein and Peptide Aggregation Tungsten Issues **Solutions** • If possible harmful extractable % to reduce • If product Ph is very high then go for Polymeric vial. • If possible change the formulation of the product.
	Problems • Discolouration of product due to extractables from glass and leachable from product. **Solutions** • Use Poly glycol coating • Replace the glass cartridge by COC/COP. • Should be more careful while choosing the primary packaging material. • If possible change the formulation of the product.
	Problems • Adsorption of protein from the product • Presence of rubber particle inside the product **Solutions** • Coated rubber stopper to use • Stability need to carryout in with different kind of sterilized rubber stopper
	Problems • Bending of plunger rod during application of drugs. • Colour leaching **Solution** • Check the rigidity of the plunge Rod. • Check the Extractable of the polymeric material • Advisable to use "Transparent material" to avoid leaching of colours from plunger

Table 1

Silica flex floats into the product due to Delamination of Glass

Type of Packaging Materials	Reason for adverse reaction and solution
	Problems • Use of high temperature in neck and along the bottom circumference of the vial. As a result these area become weak. • High Ph content of the product • Floating of silica flex into the product. **Solutions** • Reduce the flaming temperature during manufacturing of the vial. • If possible change the formulation of the product. • Use of COC/COP vial.
	Problems • Formation metal oxide during insertion of needle into the syringe. • Delamination of inner surface of the syringe. **Solutions** • If possible harmful extractable % to reduce • If product Ph is very high then go for Polymeric vial. • If possible change the formulation of the product.

Table 2

Extractable and leachable from "Polymeric Vial, syringe Needle and cartridge.

Type of Packaging Materials	Reason for adverse reaction and solution
	Antioxidants Assure protection against thermal and oxidative degradation during processing and during environmental exposure.
	Plasticizers **Typical Plastic additives** Additives, anti oxidents, stabilizers, plasticezers, emulsifiers, colourants, monomars, oligomers residual catalists, impurities UV absorvers fillers, anti fogging, anticrobials etc Lubricants, antistatic agents, initiators, stabilizers, impact modifiers, antioxidants, bactericides catalysts., blowing agents, processing aids, plasticizers, colourants, brighteners, release agents, vulcanizing agents
	**Needle for Syringe** **Problems:** • During insertion of Needle into the syringe, tungsten oxide formed. • Sometimes corrosion observed **Solutions** • Need to reduce needle insertion temperature • Advisable to use steel needle.

Table 3

Primary packaging material is not compatible with ophthalmic product.

Polymers and it's standard extractable(metal) values

Acceptance criteria for E/L study in different media (one specific example)

Type of Packaging Materials	Reason for adverse reaction and solution
	Typical Plastic additives: Additives, anti-oxidants, stabilizers, plasticizers, emulsifiers, colourants, monomers, oligomers residual catalysts, impurities UV absorbers fillers, anti-fogging, anticrobials etc. Lubricants, antistatic agents, initiators, stabilizers, impact modifiers, antioxidants, bactericides catalysts., blowing agents, processing aids, plasticizers, colourants, brighteners, release agents, vulcanizing agents **Carbonic acids:** C1, C2, C3 C2 – C5 –Aldehydes, Ketones, BHT derived from Irganox 1010, 1076 (BHT: 3,5-di-tert-butyl-4-hydroxytoluol), 2,5-di-tert-butyl benzene and 2,5-di-tert-butyl phenol from Irgafos 168.
	Problem • Colour change of the product before shelf life • Colour leaching from primary packaging materials. • Improper dispensing of the product **Solution** • Right selection of primary packaging material is a must. • Carryout stability studies properly. • Carryout extractable and leachable testing of primary packaging material. • Meter dose "Nozzle to use".
	Typical Plastic additives Additives, anti oxidents, stabilizers, plasticezers, emulsifiers, colourants, monomars, oligomers residual catalists, impurities UV absorvers fillers, anti fogging, anticrobials etc Lubricants, antistatic agents, initiators, stabilizers, impact modifiers, antioxidants, bactericides catalysts., blowing agents, processing aids, plasticizers, colourants, brighteners, release agents, vulcanizing agents

Table 4

Sl#	Polymer	Analytics /Extract	Component / Level [ppm]
a	PE	ICPMS, ICP-OES microwave digestion	Mg / 0,5 Si / 16,0 Ca / 32 Zn / 1,8
b	LDPE	ICPMS microwave digestion	Mg / 2,3 Al / 8,9 Mn / 0,01
c	PVC	ICP-OES, Al / 0,2 / Extraction with 5% acetic acid 2h 122°C	Al / 0,2 Ca / 0,4 Si / 0,9 Zn / 0,4
d	Perfluoro-elastomer	ICP-MS, IC /water 4 weeks 80°C	F / 1,1 Metals < 0,1 TOC 1,54

Table 5

Compounds	Analytes	Quantification limit (ppb)
Elements	Mg	50.0
	Al	10.0
	Cr	10.0
	Mn	10.0
	Fe	10.0
	Ni	10.0
	Cu	10.0
	Zn	50.0
	Cd	2.0
	Sd	2.0
	Pb	2.0

Table 6

Compounds	Analytes	Quantification limit (ppb)
Antioxidants and UV absorbers	2, 2- methylene- bis(4-methyl-6-tert butyl-phenol)	10.0
	2,6-di-tert-butyl-4-sec-butylphenol	5.0
	2,6-di-tert-butyl-N, N- dimethylamino-p-cresol.	10.0
	2,4-dihydroxy benzophenone.	5.0
	2-hydroxy-4-octyloxy benzophenone	5.0
	2-hydroxy-4-methoxy benzophenone	5.0
Ethylene oxide and propylene oxide	Ethylene oxide	0.5
	Propylene oxide	0.5
plasticizers	Butylated hydroxyl toluene	0.2
	2- Butanone peroxide	0.2
	Di Butyl Phthalate	0.2
	4,4- Isoprpyledene di phenol	0.2
	Benzyl Butyl Phthalate	0.2
	Di(Ethylene Glycol) Dibenzoate	0.2
	Bis(ethyl hexyl) phthalate	0.2

Table 7

Polymers are typically classified by different Criteria

Origin	Natural Polymers, Synthetic Polymers
Chemical composition	Organic Polymers, Inorganic Polymers
Thermo elastic properties	Elastomers, Thermoplastics, Thermosets
Route of synthesis	Chain-growth and step-growth polymers
Number of monomers	Homo-Polymer, Co-Polymer

Table 8

Risk Assessment

Solvent	Possible Migrants	Risk
Aqueous	Mostly Inorganics	low
Aqueous Buffer w/ 20% Tween 80	Inorganics, Siloxanes, Monomers	Moderate
Oil Based or High Organic	Monomers, Siloxanes	high

Table 9

Contamination of inhaler product due to “Extractable and Leachable”.

Type of Packaging Materials	Reason for adverse reaction and solution
	Problem • Colour leaching from primary packaging materials. • Improper dispensing of the dose. • Pressing switch is not working properly. **Solution** • Right selection of primary packaging material is a must. • Carryout stability studies properly. • Carryout extractable and leachable testing of primary packaging material • Device validation is a must before launching of the product..

Table 10

Infusion contaminated due to extractables from Tube.

Type of Packaging Materials	Reason for adverse reaction and solution
	Problem • Colour leaching from primary packaging materials. • Improper dispensing of the product **Solution** • Right selection of primary packaging material is a must. • Carryout stability studies properly. • Carryout extractable and leachable testing of primary packaging material • Device validation is a must before launching of the product..

Table 11

Wrong selection of Polymer in "Nitrocellulose patch.

Type of Packaging Materials	Reason for adverse reaction and solution
	Problems • Layer separation observed • Laminate is not passed properly on the skin. • Colour leaching **Solutions** • Layer separation and Elongation strength need to check during development stage. • Carryout extractable and leachable testing of primary packaging material

Table 12

Wrong design of "Auto injector"

Type of Packaging Materials	Reason for adverse reaction and solution
	Problem • Improper dispensing of the product • Pressing button is not working properly. • Improper dispensing of Dose. • Needle bends **Solution** • Adequate trial need to take during development stage. • Carryout stability studies properly. • Carryout extractable and leachable testing of primary packaging material • Device validation is a must before launching of the product..

Table 13

Tablet/capsule colour change in blister pack due to Extractables from Primary Packaging Material.

Type of Packaging Materials	Reason for adverse reaction and solution
	Reasons • Leaching from capsule shell • Primary packaging material is not compatible with capsule shell **Solutions** • Select correct Primary packaging material and carryout stability study correctly. • Find out what are those extractables and proceed for Alternate packaging materials.

Table 14

Wrong instructions in Package insert

Type of Packaging Materials	Reason for adverse reaction and solution
	Problems • Wrong dosage information printed • Inadequate subject matter expertise • Cut text • Improper checking during proof reading of the text matter. **Solutions** • Instructions in Packaging insert has to check and approve my "Doctor" • During proof regading necessary correction has to take if ant printing mistakes observe.

Table 15

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