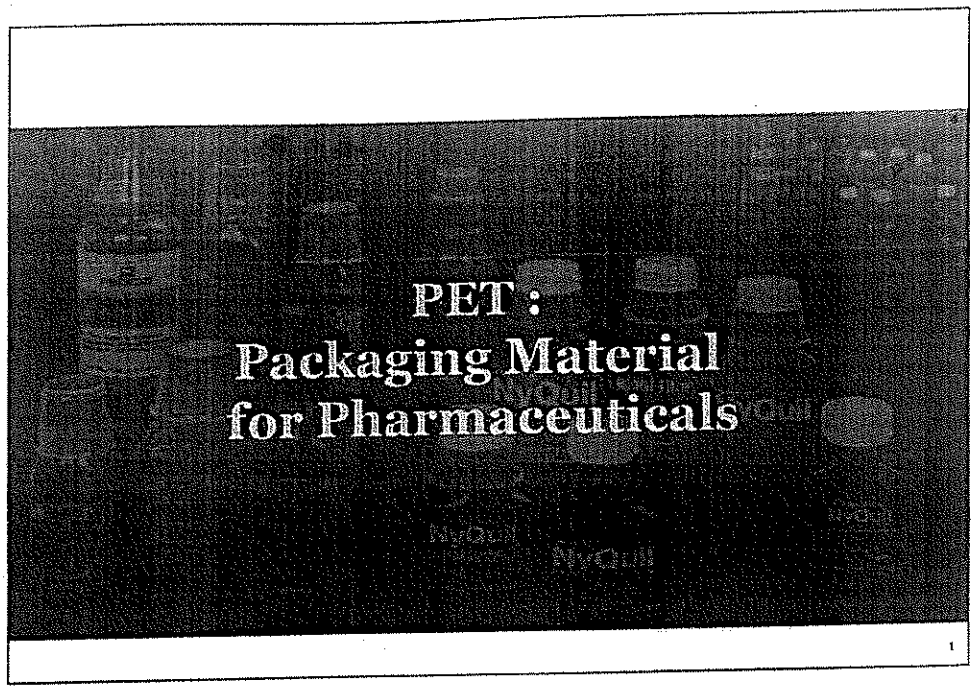
ANNEXURE 6

PRESENTATION BY PCMA



Section 1 :

WHO inputs for Packaging of Pharmaceuticals

Source :

1]
CPH Training:
Packaging Overview and tips for assessment
Andrew Chemwolo, Technical Officer
WHO Prequalification Team – Medicines Assessment
May 2014

2]
Training workshop:
Pharmaceutical development with focus on paediatric formulations
Dr. Simon Mills
21 to 25 June 2010

World Health Organization

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Types of containers: Bottles

- Glass
  - Type 1: borosilicate, most inert, has high hydrolytic and thermal shock resistance
  - Type 2: treated soda lime glass, more susceptible to leaching than type 1 glass, moderate to high hydrolytic resistance
  - Type 3: traditional soda lime glass. Has more leachable oxides than type 2 glass and moderate hydrolytic resistance
  - May be coloured to provide light protection

World Health Organization

Types of containers: Bottles

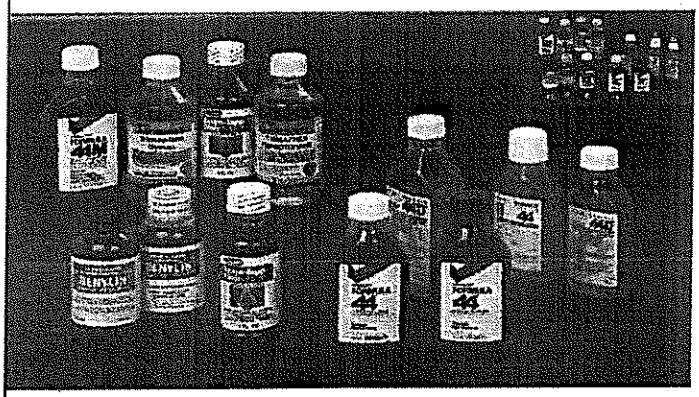
- HDPE bottle
  - in general considered highly protective
  - has good safety profile
  - Semi-permeable for liquid preparations
  - permeability also depends on wall thickness
  - naturally translucent
- PET (Polyethylene Terephthalate or Polyester) bottle
  - usually for liquid preparations
  - has good gas and fair moisture barrier properties
  - has good safety profile

World Health Organization

Types of containers: Bottles

- Polypropylene (PP):
  - used primarily for jars and closures
  - provides a rigid package with excellent moisture barrier
- Closures
  - polypropylene screw /CRC caps
  - inner seal – e.g. Induction seal/heat seal
  - aluminium cap
- Fillers, absorbents and moisture adsorbents
  - absorbent cotton
  - rayon fibres
  - silica gel desiccant or molecular sieve

World Health Organization



Section 2 : Basic chemistry of PET

Several types of plastics, each with different chemistry

Resin Identification Code		Type of plastic polymer	Monomers
Option A	Option B		
1 PETE	01 PET	Polyethylene Terephthalate (PETE, PET)	Terephthalic acid + isophthalic acid + Ethylene glycol (or MEG)
2 HDPE	02 PE-HE	High-density polyethylene (HDPE)	Ethylene
3 V	03 PVC	Polyvinyl chloride (PVC)	Vinyl Chloride monomer (VCM)
4 LDPE	04 PE-LD	Low-density polyethylene (LDPE)	Ethylene
5 PP	05 PP	Polypropylene (PP)	Propylene
6 PS	06 PS	Polystyrene (PS)	Styrene
7 OTHER	07 O	Other plastics [often Polycarbonate (PC) or Acrylonitrile butadiene styrene (ABS)]	PC: Bisphenol-A + Diphenyl carbonate or Phosgene ABS: acrylonitrile + butadiene + styrene

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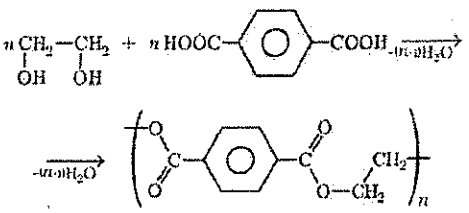
PET : simple and safe chemistry

PET does not contain any hazardous chemicals – neither are they used during their conversion into bottles

PET does NOT contain :

- **Orthopthalates (e.g. DEHP)**
- **Heavy metals** (like Cd, Cr, Pb, As, Hg)
- **Bisphenol-A**



8

PET– General Industrial Process

PET is stable at high temperatures and is a simple material to process

- **Polymer formation**
  - Continuous process = melt is fed to the melt extrusion units **(280-290°C)**
  - Batch process = polymer is solidified and chipped,
    - chips are then dried, and
    - fed to solid-state polymerisation units for further polymerization **(210-220°C)**
- **Shape formation**
  - Injection moulding (preforms) **(300°C)**
  - blow moulding (bottles) **(95-130°C)**
  - Film casting **(240-300°C)**

Note :

a) no processing aids are needed nor added

b) PET is used to make stiff & rigid containers, hence adding of any plasticizers will actually be counterproductive

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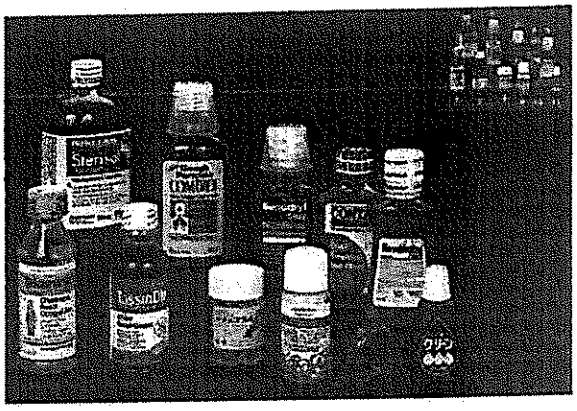
Section 3 : PET packaging for Pharma : fallacies & facts



PET (POLYESTER) HAS BEEN AROUND FOR >60 YEARS

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Recently raised Concerns about PET Packaging

1. Heavy metals
2. DEHP and other Phthalate based plasticizers
3. Antimony
4. Migration at high temperatures
5. Colourants
6. Bisphenol-A
7. Oestrogenic reactivity
8. PET (amber PET) is not recyclable

The above hazards are WRONGLY attributed to PET

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1. Heavy metals

Cd, Pb, etc. are NOT added in PET

- Lead, Cadmium, Chromium, Arsenic, Mercury, etc. are NOT NEEDED in the manufacture of PET resin or bottles.
- These heavy metals are, in fact, COUNTERPRODUCTIVE as they will affect the clarity of the PET bottles.
- Hence, they are not used

Cd, Cr, Hg, Pb, etc. are not used in the manufacture of PET

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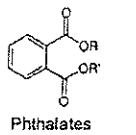
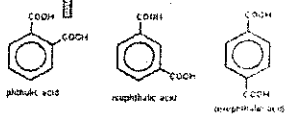
2. DEHP and Phthalate Plasticizers

PET neither contains nor needs phthalates of any kind at all



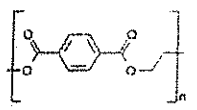
Phthalates

- PVC plastics have been assigned a recycle code "3"
- Rigid and hard articles (e.g. pipes, sheets, etc.) of PVC do not need any plasticizers
- Phthalates are used as Plasticizers in formulations for making flexible articles from PVC, e.g. medical tubings, cables, toys, etc.



ON THE OTHER HAND,

- Polyethylene terephthalate (PET), being a different plastic, has been assigned a recycle code "1"
- The terephthalate polymer PET and the monomeric phthalates (plasticizers) are **chemically different** substances
- Although the word "phthalate" appears in the name polyethylene-terephthalate, **PET does not use phthalates** for any reasons



Polyethylene terephthalate

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Carcinogenicity classification by IARC

(International Agency for Research on Cancer, France – a WHO unit)

Classification	Description	Substance	Route of Exposure	Presence in Packaging Material
Group 1	Carcinogenic to humans	Arsenic, Cadmium, Chromium (VI) & their compounds	Ingestion/ Inhalation	Glass
Group 2A	Probable carcinogens	Inorganic Lead	Ingestion	Glass
Group 2B	Possibly Carcinogenic to humans	Antimony trioxide	Inhalation	PET/ Glass
Group 3	Not classifiable as to its carcinogenicity to humans	Mercury & inorganic mercury compounds	Inhalation/ Ingestion	Glass
Group 4	Probably not carcinogenic to humans	Caprolactam	-	Nylon

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3. Antimony

Antimony leaching, if any, is well below the migration limits set by the governmental & regulatory bodies of the WORLD

- Antimony is used as a catalyst in PET resin manufacture:
  - It is used at a **very small level** of <300 ppm in PET resin.
    Also,
  - It **is completely fixed** in the polymer matrix.
- PET resins comply with Specific Migration Limit as per
  - BIS: 12252-1987 (2005)
  - US FDA 21 CFR §177.1630
  - Regulation (EU) 10/2011 on plastic materials and articles intended to come into contact with food
- Hence PET is not carcinogenic to humans in any way and thus recommended by WHO and other international regulatory bodies as safe packaging material

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4. Migration of Sb : modelling at various temperatures

Welle, F and Franz R
Food Addit Contam Part A Chem Anal Control Expo Risk Assess.
2011 Jan; 28(1):115-26.
doi: 10.1080/19440049.2010.530296.

Studies prove that even under abusive conditions, leaching of antimony from PET bottles is well below all permissible limits

- Maximum migration levels in beverages at room temperature even after 3 years of storage **will not exceed 2.5 ppb**
- Antimony can leach out at a measurable, but still very small rate at higher temperatures in excess of 150°C
- Antimony migration from PET bottles can never reach or exceed the **European-specific migration limit of 40 ppb**
- Diffusion is difficult because of the :
  - large molecular size of Antimony oxide
  - highly crystalline nature of PET bottles

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5. Colorants in PET

- **Coloured PET, when needed, is made using food colorants that are safe for humans**

These colorants

- Conform to one or more of the following regulations on colorants for food contact materials:
  - US Federal Food, Drug, and Cosmetic Act,
  - U.S. Food and Drug Administration (FDA),
  - Council of Europe (CoE) Resolution AP (89) 1
    "On the use of colorants in plastic materials coming into contact with food"
  - EU regulation 10/2011 on plastic materials and articles intended to come into contact with food.

Colorants used in Pharma PET bottles are compliant with FDA and other Food regulations

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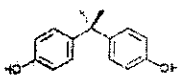
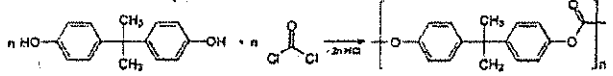
6. Bisphenol-A

Bisphenol-A (BPA) is used in Polycarbonate (resin code 07) and not in PET (resin code 01)

- BPA is used as Monomer in the manufacture of "Polycarbonate" plastics.



- BPA and phosgene react to give polycarbonate under biphasic conditions; the hydrochloric acid is scavenged with aqueous base.



- Instead of phosgene, Diphenyl carbonate may be used in which case, Phenol is eliminated instead of hydrochloric acid. This transesterification process avoids the toxicity and handling of phosgene.
- BPA-based POLYCARBONATE is clear and tough, and hence used in consumer goods, sports equipment, CDs & DVDs, clear screens

PET has a totally different chemistry than Polycarbonate and is carcinogen-free

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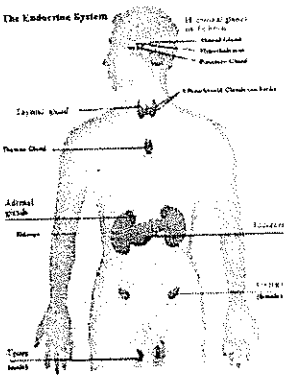
7. Endocrine Disrupting Chemicals (EDCs)

EDCs are a broad range of chemicals that interact with endocrine system of humans and animals and produce a range of adverse effects.

- **EDCs are <u>not</u> used, nor are generated by PET containers**
- They are already present in the atmosphere or in water bodies
- They are present in many commonly used products



NON-PLASTIC SOURCES OF EDCs

1. Herbicides (Atrazine) & Pesticides (DDT)
2. Pharmaceuticals:
   - Antibiotics or Contraceptives or Drugs
3. Flame Retardants
4. Detergents
5. Natural plant metabolites
6. Chemicals from cooking & burning
7. Metals (cadmium, nickel, aluminium)

PET does not contain EDCs

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8. PET : recyclability is its strength

PET is completely recyclable

RECYCLABLE

PET fibres and bottles are converted back into

- Fibres (white)
- Fibres (black or coloured)
- Strappings
- Cushions, seats
- Upholstery/curtains
- Mattresses, pillows

PET

Amber PET bottles are shred and the flakes are used in making Black fibres

Recycling of PET bottle flakes into textile products fetches Higher Premium than for making bottles

Also,
PET has lowest carbon footprint compared to Glass, Aluminium and paper

CO_2

PET is completely recycled and has the lowest CFP compared to glass, Al & paper

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Eco-impact study

Franklin Associates, USA (www.fal.com) conducted LCI on behalf of PETRA (PET Resin Association)

Single-serving container systems used for soft drinks

12 ounce Aluminum Can
8 ounce Glass Bottle
20 ounce PET Bottle

TOTAL ENERGY, SOLID WASTES AND GREENHOUSE GAS EMISSIONS FOR SOFT DRINK CONTAINERS (per 100,000 Ounces of Soft Drink)

	Energy	Solid Waste		Greenhouse Gases
	(million BTU)	weight (lbs)	(volume cu yard)	(CO_2 equivalent lbs)
Aluminum Can	16.0	767	0.95	2766
Glass Bottle	26.6	4457	2.14	4848
PET Bottle	11.0	302	0.67	1125

PET is the most eco-friendly packaging option

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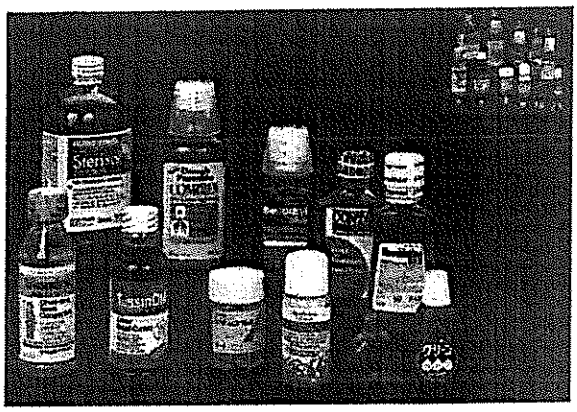
Section 4 : PET vs Glass : Bottled water & other issues



GLASS AND PET : BOTH ARE SYNTHETIC MATERIALS

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Allowable Limits of Hazardous Migrant Chemicals

Sl. No.	Migrant Chemical (leachate)	CAS No	Max possible conc. in PET leaching from PET	Leachate destination (Contents of the PET container)	Limits						
					BIS IS 10500:2012	BIS IS 13428:2005	FSSAI Regulation 2011	WHO	EU Regulation 10/2011	US EPA	Health Canada
					Drinking water	Packaged Natural Mineral Water	Food Safety & Standards (Contaminants, Toxins & Residues)				
PHTHALATES											
1	Di(2-ethylhexyl) phthalate or Dioctyl phthalate (DEHP/DOP)	117-81-7	Not Used	Water				8.0 ppb		6.0 ppb	
				Food					SML = 1.5 mg/kg		
2	Benzyl butyl phthalate (BBP)	85-68-7	Not Used	Water							
				Food					SML = 30 mg/kg		
3	Diisononyl phthalate (DINP)	14103-61-8 28553-12-0 68515-48-0	Not Used	Water							
				Food					SML = 9.0 mg/kg		
4	Total of all Phthalates		Not Used	Water							
				Food					SML(T) = 33 mg/kg		
ORGANICS											
5	Acetaldehyde	75-07-0	< 6.0 mg/kg	Water							
				Food					SML = 6.0 mg/kg		
HEAVY METALS											
6	Antimony	7440-36-0	<5.0 µg/L SML = 0.04 mg/kg	Water	No Limits	6.0 µg/L		20.0 µg/L	5.0 µg/L	6.0 µg/L	6.0 µg/L
				Food					SML = 0.04 mg/kg		
7	Arsenic	7440-38-2	Not Used	Water	10.0 µg/L	50.0 µg/L		10.0 µg/L			10.0 µg/L
				Food			0.1 mg/kg (Milk) 0.05 mg/kg (Infant Milk & foods)			5.0 µg/L	5.0 µg/L
8	Cadmium	7440-43-9	Not Used	Water	3.0 µg/L	3.0 µg/L		3.0 µg/L			
				Food			0.1 mg/kg (Infant Milk & foods)	50.0 µg/L		100 µg/L	50.0 µg/L
9	Chromium	7440-47-3	Not Used	Water	50.0 µg/L	50.0 µg/L					
				Food			0.02 mg/kg (Refined sugar)	10.0 µg/L	1.0 mg/kg in Plastic	15.0 µg/L	10.0 µg/L
10	Lead	7439-92-1	Not Used	Water	10.0 µg/L	10.0 µg/L					
				Beverages			0.5 mg/kg (Beverages)				
				Food			0.2 mg/kg (Infant Milk & foods)		2.0 mg/kg in Plastic		1.0 µg/L
11	Mercury	7439-97-6	Not Used	Water	1.0 µg/L	1.0 µg/L		6.0 µg/L			
				Food			0.25 mg/kg (All foods)				

SML = Specific Migration Limit

PET does not contain hazardous substances nor do any leachants cross the allowable limits

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Bottled water : Leaching of Antimony from Glass & PET

. Antimony (Sb) leaches out of glass as well as PET bottles
. In both cases, leaching is below internationally permissible limits

"Contamination of Bottled Waters with Antimony Leaching from Polyethylene Terephthalate (PET) Increases upon Storage"

William Shotyk and Michael Krachler,

Institute of Environmental Geochemistry, University of Heidelberg, Germany, Environ. Sci. Technol. 2007, 41, p 1560 – 1563

Major Highlight:

- In all the PET & GLASS bottles examined in this study, the Sb concentrations **were well below the limit (20 ppb)** prescribed for drinking water by WHO

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Bottled water : Leaching of Lead from Glass & PET

.. Lead (Pb) leaches out more from glass bottles than PET bottles
.. Pb is classified as carcinogen 2A, whereas Sb is only 2B by IARC.

Lead in Bottled Waters: Contamination from Glass and Comparison with Pristine Groundwater,
William Shotyk and Michael Krachler,
Institute of Environmental Geochemistry, University of Heidelberg, Germany
Environ. Sci. Technol. 2007, 41, p 3508 – 3513)

Major Highlights:

- Lead (Pb) leaching from both Glass and PET
- Leaching of Pb from **Glass bottles** is **26-57x higher than** from the PET bottles
- Bottled water in Glass containers contained Pb, whereas bottled water in PET containers contained Sb (Antimony).
- In all the bottles (both Glass and PET) the Pb level is below the maximum allowable concentration established by the WHO, EU and Canada in drinking water (10 ppb)

25

Bottled water : Leaching of other metals from Glass & PET

More metals leach out from glass bottles than PET bottles

"Bottled drinking water : Water contamination from bottle materials (Glass , Hard PET & Soft PET), the influence of color and acidification"
Clemens Reimann, Manfred Birke and Peter Filzmoser,
Applied Geochemistry, 2010, 25(7), p 1030 – 1046

Major Highlights:

- **Glass bottles leach a much longer list of elements into water:**
  - **Ce, Zr, Ti, Hf, Th, La, Pr, Fe, Zn, Nd, Sn and Cr show 7 to 24 times higher in glass bottles in comparison with corresponding PET bottles**
- Dark colored bottles (especially dark green and brown) leach more than clear bottles. This is true for both PET and Glass
- Leaching test shows that at a lowered pH of 3.5 (Acidic conditions) leaching from Glass increases considerably, often by a factor 10 or more, for most elements

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PET vs. Glass : Comparison of Packaging Materials

Sr. No.	Parameters	Polyethylene Terephthalate (PET)	Glass
1	ORIGIN	Synthetic	Synthetic
2	SAFETY		
2.1	Leaching:		
	Antimony (Sb)	Below MCL	Below MCL
	Lead (Pb)	Not Present	Below MCL
	Arsenic (As)	Not Present	Below MCL
	Other Metals	Not Present	Below MCL
2.2	Physical:		
	Breaking	Non-breakable	Fragile, Shattering creates shards
3	CONVENIENCE		
3.1	Density (g/mL)	1.35	2.5 to 8.0
3.2	Weight for 330mL bottle (g)	24	200 (8x heavier)
3.3	Squeezability	Easily Squeezable and allows controlled dispensation	Glass is Rigid
3.4	Cost	1x	2x (glass is twice expensive than PET)
4	ENVIRONMENTAL IMPACT		
4.1	Biodegradability	No	No
4.2	Carbon Foot Print in North America		
	GHG Emission/ 1000 CSD units (lbs)	315	500
	Energy Consumption/ 1000 CSD units (MJ)	3255	4227
4.3	Transportation 100mL bottles/ truck (nos.)	30,000	18,000

MCL = maximum contaminant limit

PET is more friendly to Health and Environment compared to Glass

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Glass Flaking

Delamination is a significant concern in packaging pharmaceuticals in glass

GLASS FLAKES
Dan Haines, Volker Scheumann, Uwe Rothhaar
SCHOTT pharma services

CONTRACT PHARMA • *June 2013,* pp. 92-98

In 2010, glass flakes were discovered in nine different drug products. These incidences of glass delamination, or glass attack, led to immediate recall - in one case of 30 million vials. Since that time there have been continued recalls, with glass flakes discovered in other drugs from many different manufacturers.

It typically doesn't show up until the product has been stored in the container for several months

Delamination can cause embolisms, thrombosis, or venous inflammations, foreign body granulomas, unintentional activation of the immune system

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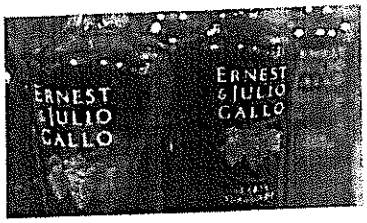
Hazardous gases used in container-glass making

Glass making process involves the use of flue gases containing Hazardous Waste dust

California's Department of Toxic Substances Control (DTSC) is suing Gallo Glass Company, for storing and recycling oil and hazardous dust containing **arsenic, lead, selenium, and cadmium** in the wine bottle making process – 4th March 2015

- Dust collected by the air pollution control device is collected and re-introduced as an ingredient in the glass making process.
- They should have been managing it properly by either sending it to a treatment or a disposal facility.
- According to Christopher Savage of Gallo Glass, other glass production companies throughout the world use the same glass making process



Gallo Glass Company faces a $25,000 fine per day for each violation.

http://www.inquisitr.com/1894838/gallo-wine-bottle-maker-sued-by-state-for-using-lead-and-arsenic-hazardous-waste-dust/#gEK9b68bPvDcfJZ.99

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oHeraldo

The Voice of Goa — since 1900

Bogmalo Sarpanch calls for ban on glass bottles on beach

14 May, 2015

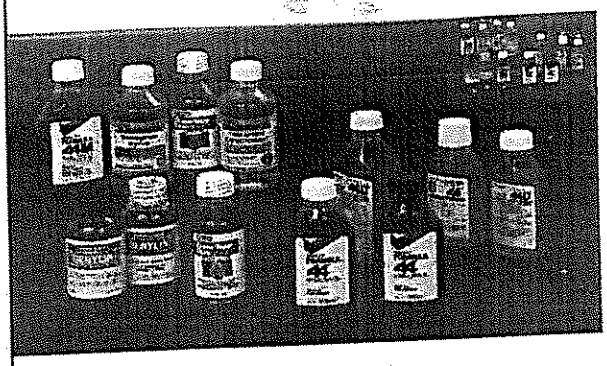
The Sarpanch of Chicolna- Bogmalo Panchayat, Laxman Kavlekar has requested the state tourism department to issue an order imposing a complete ban on the use of glass bottles on Bogmalo beach.

The demand is made in order to curb littering and the possibility of people getting hurt on the beach.

the presence of broken glass on the beach poses as a high risk to visitors. Many, including foreign tourists, have complained about receiving injuries while walking on the beach.

Seven people so far, have been injured in one week due to the presence of broken glass pieces on the beach

30



Section 5 : Safety of PET bottles : REGULATIONS & REPORTS

ENDORSEMENTS FROM GOVERNMENTS OF INDIA AND DEVELOPED NATIONS

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INTERNATIONAL Regulations allow PET for Pharma packaging

International agencies have long ago approved PET for packaging of Pharmaceuticals

INTERNATIONAL REGULATORY BODIES

- *World Health Organisation (WHO):*
  International Conference on Harmonisation, stability guidelines Q1A-Q1F
- *International Standardisation Organisation (ISO):*
  ISO 22000:2005; Food Safety Management System (FSMS) for 'Manufacture and dispatch of Polyethylene Terephthalate (PET) as raw material for food packaging applications'.

UNITED STATES GOVERNMENT

- *US FDA (Code of Federal Regulations, CFR Title 21, Section 177.1630)*
- *US Pharamocopeia (USP, Chapter 661)*

FDA U.S. Food and Drug Administration

EUROPEAN UNION

- *European Pharmacopoeia monograph (Sections 3.1.15, 3.2.2.1, 3.2.2)*
- *European Medicines Agency*

JAPAN

- *Pharmaceuticals and Medical Devices Agency*

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INTERNATIONAL Reports on PET

WHO

- Food Safety : What you should know (Section 35, p. 18, Apr 2015)

Canadian govt.

- Scientific Review of all studies on DEHP (Nov 2014)

Hanna C. Erythropel et al. Appl Microbiol Biotechnol (2014) 98:9967–9981

Spanish govt.

- Laboratory studies of 110 PET samples (May 2014)

Albert Guart, Francisco Bono-Blay , Antonio Borrell, Silvia Lacorte, Food Chemistry, 156 (2014) 73-80

International LifeSciences Institute (ILSI), Belgium

- PET for Food Packaging Applications (2000)

NAPCOR, USA

- PET Safety

Keller and Heckman, USA

- Opinion letter

All respectable international bodies have endorsed the usage of PET bottles for packaging of liquid Pharma formulations based on assessment under conditions harsher than those prevalent in India

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Pharma packaging : Indian Regulations allow PET

Indian Govt. has already permitted the use of PET for packaging of Pharmaceuticals

GOVERNMENTAL ACTS

- *Indian Drugs and Cosmetics Act (1940), Schedule M, Section 16.10 Stability studies*
- *Indian Drugs and Cosmetics Rules (1945), Schedule M, para 11 Pharmacopoeial compliance*

- **FSSA Act (2006) created the Food Safety and Standards Authority of India (FSSAI)** *formulates specifications for foods that have common features for Pharmaceuticals*

INDIAN PHARMACOPOEIA

- *IP 2014, General Chapter 6.2.3 PET containers for packaging of Pharmaceuticals*

BUREAU OF INDIAN STANDARDS

- *IS 12229-1987 (R2005) : Positive list of Constituents (PET) for their Safe use in Contact with Foodstuffs, **Pharmaceutical** and Drinking water*
- *IS 12252-1987 (R2005) : Specifications for PET for Pharmaceuticals*
- *IS 9845-1998 : Determination of Overall Migration of constituents of Plastics Materials and Articles intended to come in contact with Foodstuffs – Method of Analysis*
- *Several other Indian standards exist to control & allow PET containers for Pharma packing*

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Indian Studies on PET Bottles

These actual studies establish that PET is a safe container for Pharmaceuticals

CFTRI, Mysore

- Global Migration Studies:
  - for compliance with US FDA 21 CFR §177.1630 (2011) < 0.5 mg/in² and
  - for compliance with BIS: 12252-1987 (2005) (Extractable <10 mg/dm² and < 60 ppm)

ITRC, Lucknow

- Global Migration
- Heavy Metals
- Biological tests

CU Shah College of Pharmacy, Mumbai

- Stability study on a Cough syrup in Plastic Containers

Indian Institute of Packaging, Mumbai

- Global Migration

Italab Pvt. Ltd., Mumbai

- Systemic Injection test
- Intracutaneous test

Intertek, Mumbai (Nov 2014)

- Heavy metals

Shriram Institute for Industrial Research, New Delhi (Nov 2014)

- Heavy metals

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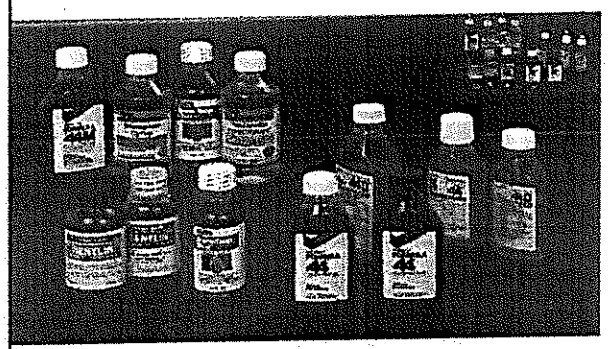

Section 6 : PET in life support : INTERNATIONAL PRACTICES

PET : ONE OF THE MOST BENIGN PACKAGING & LIFE SUPPORT MATERIALS

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PET containers are used Globally for Pharma packing – by international companies and brands

Sr. No.	Brand	Manufacturer	Remark/Type
1	Alka Seltzer	Bayer	Sinus/congestion relief
2	Benadryl	McNeil Consumer Healthcare	Sinus/congestion relief
3	CVS	Church & Dwight Co.	Antacid
4	Delsym	Wallgreens	congestion relief
5	Equate	Walmart	Cough Syrup/Antacids
6	Imodium	McNeil Consumer Healthcare	Diarrheal
7	Li'l Critters	Vitafusion	Vitamins
8	Listerine	Johnson & Johnson	Antiseptic Mouthwash
9	Little Fevers	Wallgreens	Fever Relief
10	Mucinex	Reckitt Benckiser	congestion relief
11	Nature Made	Pharmalite LLC	Vitamins
12	Nurofen	Reckitt Benckiser	Ibuprofen
13	Nyquil	Vicks (P&G)	Cough Syrup
14	Pepto-Bismol	Procter & Gamble	Stomach upset relief
15	Phillips	Bayer	Milk of Magnesia
16	Robitussin	Pfizer	Cough Syrup
17	Sudafed pe	McNeil Consumer Healthcare	Cough/Degongestant
18	Tamiflu	Roche labs	Flu treatment
19	Trojan	Church & Dwight Co.	Personal Lubricant
20	Tylenol	Johnson & Johnson	cold and Flu

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WHO Prequalified products in Liquid Orals

PET bottles are internationally used for packing liquid formulations meant for the most vulnerable (immuno-deficient) populations

Therapeutic area	INN	Formulation and strength	Applicant	Manufacturing site	Packaging	Date of PQ
HIV	Abacavir (as sulfate)	Oral solution 20mg/ml	Meditab Specialities Pvt Ltd	Satara, Maharashtra, India	PET 100ml	2012-May-02
HIV	Lamivudine	Oral solution 10mg/ml	Cipla Ltd	Goa, India; Indore, SEZ, Pithampur, Dist Dhar (M.P.), India	PET bottle 100ml; HDPE bottle 240ml (USFDA)	2002-Mar-20
HIV	Lopinavir + Ritonavir	Oral solution (80mg + 20mg)/ml	Abbott Laboratories	Queenborough, Kent, UK	PET bottle 60ml	2002-Mar-20
HIV	Nevirapine	Oral suspension 50mg/5ml	Cipla Ltd	Cipla Ltd, Goa, India; Meditab Specialties Pvt Ltd, Maharashtra, India; Indore, SEZ, Pithampur, Dist Dhar (M.P.), India	Amber coloured PET bottle 100ml, 240ml; Amber coloured glass bottle 25ml, 10ml	2009-May-25
HIV	Ritonavir	Oral solution 80mg/ml	Abbott Laboratories	Queenborough, Kent, UK	PET bottle 90ml	2002-Mar-20
HIV	Zidovudine	Oral solution 50mg/5ml	Combino Pharm S.L	Medea, Barcelona, Spain	PET bottle 200ml + syringe 10ml	2004-Jan-01
HIV	Zidovudine	Oral solution 50mg/5ml	Meditab Specialities Pvt Ltd	Maharashtra, India	PET bottle 100ml	2011-Nov-15
TB	Para-aminosalicylate sodium	Delayd release granules 60% w/w	Macleods Pharmaceuticals Ltd	Kachigam, Daman, India; Solan, Himachal Pradesh, India	LDPE bag placed in triple laminated Alu/PET/Alu/LLDPE sachet further packed in HDPE container 100g; PET/Alu/LLDPE Sachet 9.2g	2009-Dec-14

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PET in Medical Field

Not just packing of Pharmaceuticals, but PET is safe in more critical and permanent human implants

US FDA:

FDA standard 21CFR 878.5000 has approved the following medical devices containing PET as **safe and effective** when used for

- ***soft tissue approximation and/or ligation, including***
- ***cardiovascular, ophthalmic and neurological tissue.***
- ***surgical sutures***
- ***oesophageal and gastrointestinal dialators***
- ***patches, pledgets and intracardiac devices (surgical mesh)***

- **394 PET-based products are in use in medical field for several decades**
- **98 PET-based products in ophthalmic applications**
- **Several PET-based products in use as implants**

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PET in Medical Field (Example)

Commercial PET-based medical devices have obtained DMF nos. testifying compliance and safety

Thermo Fisher SCIENTIFIC

Tel 585-586-8800 Fax 585-899-7605
75 Panorama Creek Drive, Rochester, NY 14625

Product Certificate
Thermo Scientific
Nalgene and Nunc Products

Thermo Fisher Scientific hereby certifies that the product identified below is produced, inspected and found to be in compliance with product and quality specification requirements as documented in our ISO 13485:2003 Quality Management System (QMI-SAI Global File No. 1606319 and 1606321) in the USA.

Lisa Adams

Certificate issued: 04/28/2012

The following information represents Product Certification for: Item# 342040-0650

Description BTL,SQ,PET,650ML,W/CLOS,STER|| Lot# 1089289 Use Before 04/28/2017 Manufactured 04/13/2012

Part Number	Description	Common Name	DMF#	Cytotoxicity	USP Class VI	FDA Compliance - 21 CFR
1-0650-SBP	BTL,SQ,650ML,SQ,NAT,PET	COMPONENT PART				
8-0003-51	RESIN, PET 1506M	PET, 1506M	15205	PASSED	PASSED	177.1315(b)(1) and 174.5
1-1603-20	CLOS,38/430,HDPE,NAT,NALGE	COMPONENT PART				
8-0012-01	RESIN,HDPE,INJ	HIGH-DENSITY POLYETHYLENE	1646	PASSED	PASSED	176.170(c), 177.1520(c)(3.2a

If N/A appears in any of the columns above it means the information is not available. Any item listed as "COMPONENT PART" will show blank in the DMF# Cytotoxicity, USP Class VI and FDA Compliance Information columns.

If the word "PASSED" appears in the USP Class VI column next to the resin listing, this material has passed USP Class VI requirements, latest Volume, as part of our initial test approval protocol.

If the word "PASSED" appears in the Cytotoxicity column next to the resin listing, this material was tested and shown to be non-cytotoxic as part of our initial test approval protocol, using either mouse fibroblast L929 cells or the more sensitive human diploid lung cell lines WI-38 or MRC-5

Product was Gamma Irradiation Sterilized. Product was dosimetric released per ANSI/AAMI/ISO 11137 guidelines. Product was determined to be non-pyrogenic at a level < 0.5 EU/ml as by "Guidelines on the Validation of the Limulus Amebocyte Lysate Test," as defined by the FDA (12/87), as an end product endotoxin test for human and animal parenteral drugs, biological products and medical devices.

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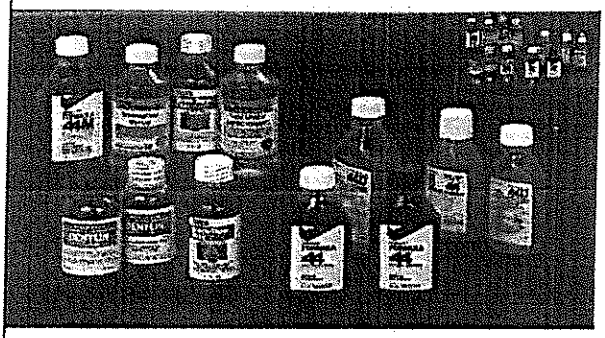

Section 7 : PET's Safety & versatility : SUMMARY

INDIA NEEDS TO REMAIN COMPETITIVE BY MAINTAINING BEST INTERNATIONAL PRACTICES

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Recycle Codes of various Plastics & their end uses

Plastic Identification Code	Type of plastic polymer	Monomers	Typical End Uses
01 PET	Polyethylene terephthalate (PET, PETE)	Terephthalic acid + isophthalic acid + Ethylene glycol (or MEG)	Bottles, Containers, Jars, Films, Strappings, Fiber and Filaments, Non-wovens, Medical devices etc.
02 PE-HD	High-density polyethylene (HDPE)	Ethylene	Hair-oil & other household containers, Packaging films, furniture, Pipes, Fuel tanks, etc.
03 PVC	Polyvinyl chloride (PVC)	Vinyl Chloride monomer (VCM)	Wire and cables, Footwear, Floorings, Packaging films, Pipes and fittings, Medical devices, Tarpaulins, toys, etc.
04 PE-LD	Low-density polyethylene (LDPE)	Ethylene	Milk pouches, Containers, packaging films tubings, Furniture, etc.
05 PP	Polypropylene (PP)	Propylene	Chairs, Furniture, Containers, Packaging films, Automotive and Electronic components, Textiles, Medical devices, Aerospace Applications, etc.
06 PS	Polystyrene (PS)	Styrene	Protective packaging applications, Disposable cups and containers, Foams, Insulations, etc.
07 O	Other plastics (often Polycarbonate (PC) or Acrylonitrile butadiene styrene (ABS))	PC: Bisphenol-A + Diphenyl carbonate or Phosgene ABS: acrylonitrile + butadiene + styrene	PC: Electronic, Aircraft, Security and Automotive components, Construction industries, Data Storage applications ABS: Electronic and Automotive components, Pipes, Instruments body parts, etc.

Each plastic has a different chemistry

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PET : has been around for a long time, the world over

PET fibres being made for more than 65 years

PET bottles
- have been made for more than 42 years
- manufactured all over the world
- more than 300 million MT already used globally
- more than 15 trillion bottles packed and consumed

NO EPIDEMIOLOGICALLY ADVERSE OBSERVATION GLOBALLY
- No case reported on any occupational hazards faced by the work-force (inhalation ingress)
- No case of health effects on civilian consumers (oral ingress)
- No case of health effects due to draping garments (dermal ingress)
- Not a single clinical evidence correlating any ailment with PET chemistry

PET is one of the SAFEST materials 43

The Safety Ecosystem of PET Packaging

U.S. Food and Drug Administration · USP U.S. Pharmacopeia The Standard of Quality · pira · CE · fssai Food Safety and Standards Authority of India · cftri · BPA FREE · RECYCLABLE · CO_2 · 1 PET

PET has been around for over 60 years

More than 300 million MT already used globally

More than 15 trillion bottles packed and consumed

NOT A SINGLE CLINICAL OR EPIDEMOLOGICALLY ADVERSE OBSERVATION GLOBALLY

PET has the widest possible acceptance for any packaging material 44

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Lobbying against PET : list of rejected PILs

#	PIL No.	Petitioner	Court	PIL Dismissal Date
1	12847/2013	Sri Saidatta	The High Court , Bengaluru	24-04-2013
2	54857/2012	Parivartan Foundation	The High Court, Allahabad	09-05-2013
3	2509/2013	Prani Mitra Samiti	The High Court, Jabalpur	26-06-2013
4	2518/2013	Prem Singh	The High Court, Chandigarh	02-08-2013
5	44/2013	Vaayu Vision Educational Society	The High Court, Hyderabad	02-09-2013
6	ECD/07/Gen/2013	Sri Saidatta	The Court of Excise Commissioner, Bengaluru	17-09-2013
7	31833/2013	Prani Mitra Samiti	The Supreme Court, New Delhi	25-10-2013

The courts have dismissed all petitions and have reprimanded petitioners for not exercising due diligence before seeking a ban on PET bottles

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PET : the preferred packaging material for Liquid Pharma products

1. PET is made from simple and safe chemicals viz. PTA, IPA, MEG and catalysed by very small amounts of Sb_2O_3 and hence considered as a safe packaging material by WHO
2. PET does not contain heavy metals, phthalates, Bisphenol A or other Carcinogens or EDCs (WHO report, April 2015)
3. No adverse Epidemiological evidence in PET's entire existence of 42 years globally
4. PET bottles comply with International & Indian Pharmacopeias & EU, USFDA, Japan+ regulations
5. Actual testing in various accredited Indian Labs (CFTRI, IITR, Intertek) confirms safety of PET bottles
6. ILSI, WHO, reviews and reports by European universities, law firms, research institutes safety of PET bottles for usage in Pharma, Food and all other applications.
7. All major international pharma companies use PET bottles for packing liquid formulations meant for pediatric, female and geriatric populations
8. Globally, PET is the most preferred packaging material being safe, shatterproof, lightweight and environmentally friendly

Packaging of all liquid Pharma products in PET bottles is SAFE & CONVENIENT

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THANK YOU