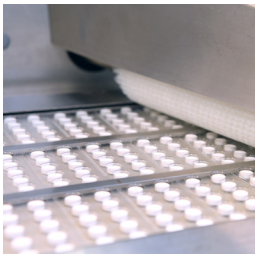
efpia

European Federation of Pharmaceutical Industries and Associations

White Paper on pharmaceutical packaging





What is Pharmaceutical Packaging?

The pharmaceutical sector is one of the most regulated in Europe and the world, operating effectively within an evidence-based framework to maintain the highest standards, ensuring packaging never compromises patient safety or product effectiveness. The purpose of pharmaceutical packaging is to contain, protect, transport, and identify drug products until patient administration and/or use, and to include relevant information for safe and efficacious product use. User-friendliness for patients and safety of use (i.e., child-resistant closures) are also important elements in designing primary packaging in contact with medicines.

Pharmaceutical packaging[1] plays a critical role in multiple manufacturing steps that a medicinal product has to undergo in order to become a finished product, including the filling and labeling processes. The pharmaceutical packaging system that contains and protects the finished product is referred to as the container closure system, which is the sum of packaging components that together contain and protect the dosage form (ICH Q1A[2]). The packaging system includes both the immediate packaging components that are in direct physical contact with the active pharmaceutical ingredient or finished drug product and outer packaging components that contain the immediate package and are intended to provide additional protection to the drug product (EU Medicinal Product Directive, 2001/83/CE[3]).

Other global systems, such as The Wiley Encyclopedia of Packaging Technology[4], identify primary, secondary, and tertiary packaging subsystems of pharmaceutical packaging, where primary packaging is defined as materials in direct physical contact with the active pharmaceutical ingredient or finished product. Secondary packaging refers to additional packaging beyond the actual container in which a medicinal product is stored and normally consists of non-contact packaging materials. Examples include printed or unprinted cartons, labels, leaflets or inserts, overwraps, and transit containers such as folding boxes. Tertiary packaging protects the product and the packaging during storage and distribution environments. Tertiary packaging usually includes corrugated shipping containers, gaylord containers, and pallets.

There are several materials and formats used for pharmaceutical packaging, including different types of plastics, glass, aluminum, paper board, etc.

Pharma packaging types

Primary Packaging

In direct contact to the drug product.

Secondary Packaging

Protects[5] and collate the product and carries information and branding.

Is typically the sales unit:

- Cartons
- Leaflets
- Product Labels
- Carton labels

Tertiary Packaging

Facilitates the protection, handling and transportation of a series of sales units.

- Shipping boxes
- Shipping labels

1 https://cdn.who.int/media/docs/default-source/medicines/norms-and-standards/guidelines/regulatory-standards/trs902-annex9.pdf?sfvrsn=82b4c57d_2

2 https://database.ich.org/sites/default/files/Q1A%28R2%29%20Guideline.pdf

3 https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2001:311:0067:0128:en:PDF

4 https://onlinelibrary.wiley.com/doi/book/10.1002/9780470541395

5 Secondary packaging is often used to provide additional barrier to primary packaging i.e. Silica gel sachets or UV barrier through opaque secondary packaging.

Regulatory and Technical Specifications for Pharmaceutical Packaging

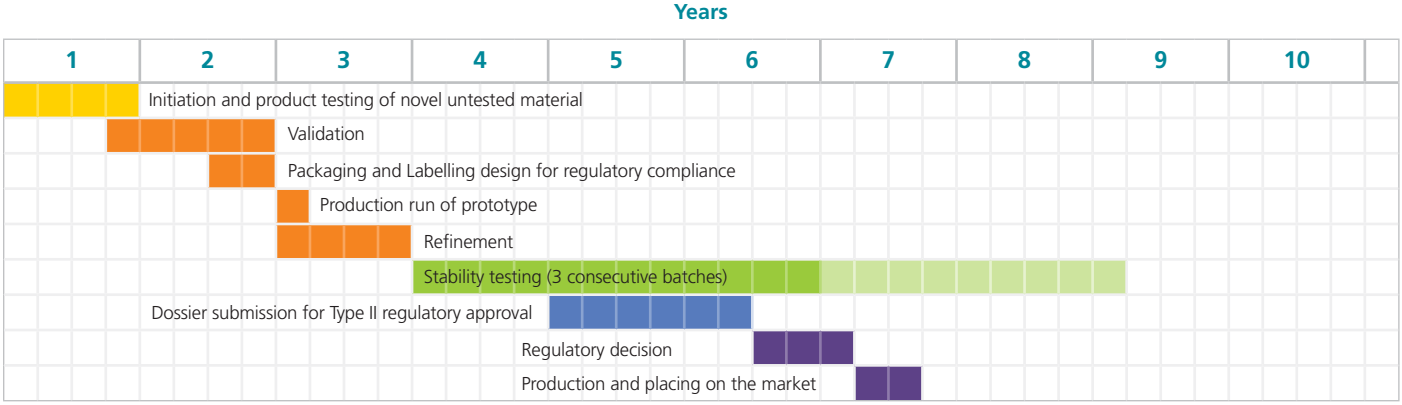
1) Regulations for drug product packaging

The pharmaceutical industry is a highly regulated industry. Regulatory oversight is a means to ensure the quality of drug products and, ultimately, the safe and effective use of drug products by patients. To meet the regulatory requirements, it is the responsibility of the pharmaceutical manufacturer to design, develop, and validate their products in accordance with a quality management system. The production process for the drug product and its packaging must be conducted under good manufacturing practice (GMP)[6], which includes batch control, process validation, and process qualification. Adherence to GMPs minimizes risks to the product and subsequent risks to patients' health. When an application for a medicinal product is submitted to a regulatory agency, such as a Marketing Authorization Application to the European Medicines Agency (EMA)[7,8], or a New Drug Application to the Food and Drug Administration (FDA), the manufacturer must include documentation regarding the immediate and outer packaging subsystems in the application.

For key examples of the regulatory guidance documents and requirements governing the various aspects of drug product packaging, refer to Annex 1 of this document.

The EU environmental regulatory landscape is evolving rapidly, and there is also interplay with pharmaceutical regulatory requirements. As pharmaceutical products have a long development time and making changes can take several years, alignment between these two regulatory spheres and the early publication of detailed guidance in delegated acts, e.g., for the EU Packaging and Packaging Waste Directive[9] (soon to be replaced by the Packaging and Packaging Waste Regulation), are key to ensuring EFPIA members can develop and implement strategies responding to this dynamic landscape in time.

Figure 1: Typical process flow for the introduction of a new Immediate Packaging Material in the first market: additional markets require up to 2 years more



6 https://www.who.int/publications/i/item/WHO_TRS_823

7 https://www.ema.europa.eu/en/human-regulatory-overview/research-development/compliance-research-development/good-manufacturing-practice

8 https://health.ec.europa.eu/system/files/2023-09/2018_packaging_guidelines_en_1.pdf/

9 https://environment.ec.europa.eu/topics/waste-and-recycling/packaging-waste_en

2) Technical specifications for pharmaceutical packaging

To meet the regulatory requirements, United States Pharmacopeia (USP)[10] and European Pharmacopoeia (Ph. Eur.)[11] grade materials are used when developing pharmaceutical packaging that will be in direct contact with medicinal products. The materials must be compatible with the drug product and its intended use, which is demonstrated through regulated testing standards.

Additionally, the immediate packaging system for the drug product is often required to maintain sterility over the product shelf-life, in particular for injectable products. Pharmaceutical packaging often require Child Resistance features provided in primary or secondary packaging based on requirement and formats. The secondary packaging system requires proper labeling and serialization for functions such as identification and anti-counterfeit protection and often requires tamper evidence and child-resistant features. Thus, compared to other industries, such as cosmetics, food, and consumer products, pharmaceutical packaging has more stringent requirements.

Common Packaging & Drug Delivery Systems

Examples of common primary packaging materials currently in use are shown below (full chemical names for the listed materials are provided in final annex of the document).

Blister pack

Common use: Oral dose tablets and capsules, where the user accesses the medication by pushing the individual dose through the foil lid.

Typical materials of construction: Aluminum cold form, and thermofomed plastics (PVC, PET, PP and barrier materials consisting of COC, PVDC, PCTFE) with aluminum lidding stock.

Rationale: The use of plastics allows for mono-material or multi-layer thermoformable films to achieve high-barrier properties while maintaining biocompatibility and regulatory requirements for direct product contact materials. Plastic blister packs offer superior protection against moisture and/or oxygen, and they can be easily customized for different products.

Bottle pack

Common use: Products in tablets and liquid format (may provide sterile environment by induction sealing).

Typical materials of construction: Glass, plastic (PET, HDPE, COP, COC) and aluminum.

Rationale: The use of plastics is preferred to glass alternatives due to their lightweight, durability, and cost-effectiveness. These attributes reduce breakage during transportation and handling, reducing waste and the potential for contamination.

Borosilicate glass vials and ampules

Common use: Drugs for injection and intravenous therapy (may be crimp sealed with rubber stopper and aluminum cap).

Typical materials of construction: Type I, Type II and Type III glass, defined by the raw material content and material characteristics.

Rationale: The use of Type 1 borosilicate glass vials and ampules is preferred due to the superiority in thermal and chemical resistance properties.

Pouch packaging

Common use: Sterile device packaging and functional barrier property packaging.

Typical materials of construction: Aluminum, laminated plastic (PVC, HDPE, PET, LDPE, PU, PP) and Tyvek (HDPE).

Rationale: The use of plastics allows for multi-layer sealable films to achieve high-barrier properties while maintaining biocompatibility and regulatory requirements for direct product contact materials. Plastics in pouches offer superior protection against moisture and/or oxygen, offer microbial barriers in sterilized applications, and they can be easily customized for different products.

Tube packaging

Common use: Semi-liquid formulation of cream.

Typical materials of construction: Laminated or coextruded plastic (PP, PE, EVOH) and aluminum.

Rationale: The use of plastics allows for mono-material or multi-layer thermoformable films to achieve high-barrier properties while maintaining biocompatibility and regulatory requirements for direct product contact materials. Plastic tube packs offer superior protection against moisture and/or oxygen, and they can be easily customized for different products.

10 https://qualitymatters.usp.org/usp-qa-standards-plastic-packaging-systems-drug-products

11 https://www.edqm.eu/en/d/114739?p_l_back_url=%2Fen%2Fsearch%3Fq%3Dpackaging%26sort%3Dtitle%26voc256731%3D257293

Based on a survey across the pharmaceutical industry, the most common types of plastic used across all packaging formats are PP, PE, PET, and PVC.

Plastics and polymers play a critical role in the quality, protection, and compatibility provided by pharmaceutical packaging. Plastics provide the capability for high-barrier materials, and multi-layer laminate films that are not possible with other materials. The supply of alternate materials is limited and challenging, and therefore, virgin fossil plastics are being used in the pharmaceutical industry to fill the void. Nevertheless, to bridge that gap, the pharmaceutical industry is collaborating with upstream suppliers to obtain sustainable materials at scale. (See section on partnerships).

Table of common plastics and their typical use

Material	Function	Typical Application
Polypropylene (PP)	Containment, sealing, flexibility of structures and formats	Bottles, closures, blisters, syringes, pouches, etc.
Polyethylene (PE)	Containment, sealing, flexibility of structures and formats	Bottles, closures, tubings, blisters, pouches, etc.
Polyvinylchloride (PVC)	Containment and flexibity of structures	Blisters, bags, tubings, etc.
Polyester Terphthalate (PET)	OTR Barrier and containment	Bottles, trays, blister, etc.
Polychlorotrifluoroethylene (PCTFE)	High Barrier	Blisters
Polyvinylidenechloride (PVDC)	High Barrier	Blisters
Cyclic olefin copolymer (COC/ COP)	High Barrier	Bottles, blisters, vials

Potential Impact of Regulatory Requirements on Packaging Development and Innovation

Quality and safety of plastic materials and how these factors may affect availability

FDA Guidance for Industry Container Closure Systems for Packaging Human Drugs and Biologics (May 1999)[12] states that post-consumer recycled plastic should not be used to manufacture a primary packaging component. If it is used for a secondary or associated component, the safety and compatibility of the material with its intended use should be addressed appropriately. The above-mentioned guidance is the only one explicitly banning the use of postconsumer recycled content, but the criteria set in existing standards and regulations are de facto achieving the same results.

Materials used for primary containers must not extract/leach contaminants, and these characteristics should be tested and regularly assessed. Extractable studies based on USP, Ph Eur, and Japanese pharmacopeia standards are conducted for every new plastic. In addition, studies need to be done throughout the entire shelf life of a medicinal product. In terms of time, effort, and cost, it would be impractical to repeat extractable/leachable studies for each new batch of recycled plastics. The requirement to test each batch for consistency and compliance would significantly affect pharmaceutical industry operations as well as the security of the supply, with negative consequences for patients' access to the medicines they need.

12 https://www.fda.gov/media/70788/download

Options Available to Pharmaceutical Companies to Reduce Environmental Impact of Packaging

1 Partnerships - Move towards recyclable packaging

Through Horizon Europe and the Innovative Health Initiative, there are opportunities to create sustainable collaborative public-private research platforms to respond to the need to lessen the environmental impact of packaging. This includes recycling of packaging materials and/or alternatives to current packaging chemicals. Priority should be given to target areas for which action could be expected in the short term (3 to 5 years). For example, increasing post-consumer recycled content in packaging or tackling excessive packaging and reducing packaging waste. Furthermore, adequate industry/government funding should be made available for start-up companies that are looking to develop the collection and recycling of post-production pharmaceutical waste, such as reclaiming aluminum. Some packaging components are integral to securing a product's safety and efficacy, including blisters, pouches, plastic liquid containers, etc., and extensive innovation would be required to generate alternatives.

Projects to develop new and effective technologies, products, and innovations that generate minimal waste throughout their lifetime of use in healthcare systems should also be considered. Such innovations could include environmentally friendly packaging materials and methods, personalized dosing, increasingly reusable and recyclable medical devices, paperless methods of delivering leaflets, and digital products and practices, to name a few.

Another important element to consider is standardizing packaging labels, ePILs (electronic patient information leaflets), and instructions for post-use recycling across all member states. Currently, significant variation between member states hampers the use of these symbols and limits the capacity to convey recycling messages to patients in our common EU market.

2 Adoption of biobased plastics

Bio-polymers from responsibly sourced renewable sources could be used, provided that they have the same quality as virgin materials and meet the criteria listed in the regulations and standards described in the previous paragraphs. Materials of natural origin, especially those on the Science Based Targets Network (SBTN) High ImpactCommodity List[13], should be carefully selected and sourced responsibly to avoid any unintended environmental consequences, for example, on biodiversity, deforestation, water use or pollution due to fertilizer use.

The application of these biobased materials to pharmaceutical products has yet to be extensively studied. Future studies should consider factors such as challenges linked to the type of formulation that would be in contact with the new material and its sensitivity to the material.

Some companies are already adopting bio-based polymers for specific products in some geographies. Availability of bioplastics and quality consistency are key prerequisites to ensure a continued supply of medicines to patients. In addition, external factors and policy changes related to the availability of sustainably sourced biobased polymers should be factored into any future mandatory requirement. For example, the food insecurity is leading some countries, such as the United Kingdom, to prioritize food production by rerouting crops initially intended for biobased products.

13 https://sciencebasedtargetsnetwork.org/how-it-works/assess/

3 Recycled content via mechanical and chemical recycling

The use of secondary raw materials in pharmaceutical packaging, especially contact-sensitive packaging, can present significant challenges due to the regulatory and safety requirements associated with our products and the technical performance needed from these materials. The pharmaceutical industry is committed to maximizing opportunities to recycle materials and to keep these materials at the highest possible value for as long as possible. Collaboration across the industry and with other industrial sectors and engagement with the EMA and FDA are essential to realize the full potential of this approach. Due to the quality and safety requirements for pharmaceutical-grade polymers, challenges remain for the use of mechanically recycled PCR plastic in pharmaceutical packaging. Some companies have started take-back programs in different geographies, and are mechanically recycling materials from used medical devices like injection pens. However, whilst the ultimate aim is to close the loop and incorporate this material in new pharmaceutical products, currently the recycled materials are used in other sectors.

Chemical recycling seems promising in potentially separating unintended contaminants and impurities. However, there is still limited evidence about chemically recycled plastics especially when it comes to traceability, maturity of technologies, and capabilities. Challenges with consistency in chemically recycled polymers have also been identified. If the same consistent quality of virgin grade can be ensured, pharmaceutical grade material from chemical recycling might be used more easily following the certification and compliance rules in place for virgin material. Availability of certified pharmaceutical-grade recycled plastics with minimal variation and consistent quality between batches as well as regulatory validation and approval, are essential prerequisites before setting mandatory targets for the sector.

4 Use of novel mono materials such as dry pulp molded materials for oral solid

New developments in mono materials for blister and lidding stock like PP, HDPE and PET are opening up pathways towards alternative blister materials which are PVC free. The addition of molded pulp technology for use in oral liquid and solid packaging applications has brought new potential for paper-based packaging. However, molded pulp packaging requires the use of laminated plastics to achieve the ability to retain liquid products or provide barrier protection for moisture and gas permeation. Further, many of these developments need to be validated and included as materials for safe use in pharmaceutical packaging as part of USP/ Ph Eur, ISO standards, and regulatory authorities, which could take several years. (figure 1).

5 Innovate along with our supply base at scale.

Any definition of recyclability must account for the specific requirements of primary packaging that comes into contact with the medicinal product. The proposal to create a list of features that would automatically characterize packaging as non-recyclable should be carefully assessed vis à vis the potential impact on primary packaging for pharmaceutical products and, as a consequence, on the supply of medicines to patients. Some materials appearing on the list are used in primary packaging, including PVC for blister packs and aerosol cans, which are essential primary packaging for pressurized metered dose inhalers used to treat respiratory diseases. Pharmaceutical companies and supply partners are actively working on identifying sustainable primary packaging materials that offer the product protection required, but viable alternatives are not yet operational. The list of exclusionary features should be limited to materials that serve no purpose in preserving the product, such as secondary packaging that does not serve a protective function or information function and tertiary packaging over a period of ten years.

6 IHI and other stimuli to drive innovation

The Commission should consider investing public R&D funds in seeking sustainable solutions to the safety issues surrounding primary packaging in medicines and other highly regulated sectors. This could support relevant initiatives under the European Green Deal. EFPIA and its members would welcome such a workstream and actively engage. The UK-based Centre for Innovation is currently drafting a proposal in this sense, and considerations are currently under the IHI. An IHI project, ENKORE, kicked off in January 2025 to look at sustainable packaging.

Partnerships

eunomia

innovative health initiative

European Commission

The European Green Deal
Striving to be the first climate-neutral continent

UK Research and Innovation

ANNEX 1

United States Regulations

US FDA CRF Title 21: regulations for Drug, Medical Device and combination products[14]

USP 7: labelling requirement for pharmaceutical product[15]

USP 1207: CCIT requirement for pharmaceutical product[16]

FDA Guidance for Industry Container Closure Systems for Packaging Human Drugs and Biologics (May 1999)[17]

USP <1661>[18], European Pharmacopoeia (v.10.8)[19], Ch 3. Pharmacopoeias define analyses/tests to be done on plastic material as primary packaging, e.g., presence of some substances (heavy metals) or additive types with specifications

USP <1663>[20] and BPOG[21]; about the detection of leachables in extraction studies

(US) 21CFR part 211.94[22]: (a) Drug product containers and closures 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.

Container Closure Systems for Packaging. Human Drugs and Biologics. Chemistry Manufacturing, And Controls[23] (FDA, May 1999)

Metered Dose Inhaler and Dry Powder Inhaler Drug Products Chemistry, Manufacturing and Controls Documentation[24] (FDA, Oct 1998)

Industry Nasal Spray and Inhalation Solution Suspension, and Spray Drug Products Chemistry, Manufacturing and Controls Documentation[25] (FDA, July 2002)

European Union Regulations

EMEA/CVMP/205/04 Guideline on plastic immediate packaging materials

MDR (Medical devices regulation)[27] annex 1 chapter 2 general requirements (chemicals, physical and micro properties of materials)

European pharmacopoeia monograph 3.2.2 plastic containers and closure for pharma use[28]

Guideline on Pharmaceutical Quality of Inhalation and Nasal Products (EMEA, June 2006)[29]

Eudralex – Volume 4 Good Manufacturing Practice Annex 1 "Manufacture of Sterile Medicinal Products"[30]

Commission Regulation (EU) No 10/2011 of 14 January 2011 on plastic materials and articles intended to come into contact with food Text with EEA relevance[31]

Global Regulations

ISO 11607 part 1 and part 2: Packaging for terminally sterilized medical devices[32]

ISO 13485: Medical devices – Quality management systems[33]

ICH Q3E Guideline for Extractables and Leachables[34]

WHO Annex 9 Guidelines on packaging for pharmaceutical products[35]

WHO Annex 9 Model Guidance for the storage and transport of time and temperature sensitive pharmaceutical products[36]

WHO Annex 10 Stability testing of active pharmaceutical ingredients and finished pharmaceutical products[37]

ICH Q8 Pharmaceutical Development[38]

14 https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?cfrpart=4
15 https://go.usp.org/USP_GC_7_FAQs?_gl=1*pywoom*_gcl_au*MTc1NzY0NDMwNC4xNzMyNTIzMTI2*_ga*MTA2MjY2MTM1LjE3MzI1MjMxMjQ.*_ga_DTGQ04CR27*MTczMjUyNTI5Ny4yLjAuMTczMjUyNTI5Ny4wLjAuMA..
16 https://doi.usp.org/USPNF/USPNF_M99926_01_01.html
17 https://www.fda.gov/media/70788/download
18 https://www.usp.org/sites/default/files/usp/document/workshops/1661_evaluation_of_plastic_packaging_systems_and_their_materials_of_construction_with_respect_to_their_user_safety_impact_pf_42.pdf
19 https://www.edqm.eu/en/-/european-pharmacopoeia-supplement-10.8-now-available#:~:text=Supplement%2010.8%20is%20now%20available,purchase%20via%20the%20EDQM%20Store.
20 https://doi.usp.org/USPNF/USPNF_M7126_03_01.html
21 https://www.biophorum.com/download/extractables-testing-of-polymeric-single-use-components-used-in-biopharmaceutical-manufacturing/
22 https://www.ecfr.gov/current/title-21/chapter-I/subchapter-C/part-211/subpart-E/section-211.94
23 https://www.fda.gov/regulatory-information/search-fda-guidance-documents/container-closure-systems-packaging-human-drugs-and-biologics
24 https://www.fda.gov/regulatory-information/search-fda-guidance-documents/metered-dose-inhaler-mdi-and-dry-powder-inhaler-dpi-drug-products-quality-considerations
25 https://www.fda.gov/regulatory-information/search-fda-guidance-documents/nasal-spray-and-inhalation-solution-suspension-and-spray-drug-products-chemistry-manufacturing-and
26 https://www.ema.europa.eu/en/plastic-primary-packaging-materials-scientific-guideline
27 https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32017R0745
28 http://www.uspbpep.com/ep60/3.2.2.%201.%20plastic%20containers%20for%20aqueous%20solutions%20for%20infusion%2090003e.pdf
29 https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-pharmaceutical-quality-inhalation-and-nasal-products_en.pdf
30 https://health.ec.europa.eu/medicinal-products/eudralex/eudralex-volume-4_en
31 https://eur-lex.europa.eu/eli/reg/2011/10/oj
32 https://www.iso.org/standard/70799.html
33 https://www.iso.org/standard/59752.html
34 https://www.ich.org/page/quality-guidelines
35 https://cdn.who.int/media/docs/default-source/medicines/norms-and-standards/guidelines/regulatory-standards/trs902-annex9.pdf?sfvrsn=82b4c57d_2
36 https://www.who.int/docs/default-source/medicines/norms-and-standards/guidelines/distribution/trs961-annex9-modelguidanceforstoragetransport.pdf?sfvrsn=b80e925f_2
37 https://www.who.int/publications/m/item/trs1010-annex10
38 https://www.ich.org/page/quality-guidelines

ANNEX 2

Abbreviation	Material
COC/COP	Cyclic olefin copolymer
EVOH	Ethylene Vinyl Alcohol Copolymer
HDPE	High Density Polyethylene
LDPE	Low Density Polyethylene
PCTFE	Polychlorotrifluoroethylene
PE	Polyethylene
PET	Polyethylene Terephthalate
PP	PolyPropylene
PU	Polyurethane
PVC	Polyvinylchloride
PVDC	Polyvinylidenechloride