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# VIRTUAL SYMPOSIUM 2021

## Large Volume Parenteral Packaging System

# Design, Manufacturing and Qualification of plastic Container Closure System

24-25 March 2021

D. SAINT ELLIER

# Presentation overview

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Company overview

LVP system application diversity and guidelines

Design challenges : combine performance, quality and safety

Customer expectations: Conformance  demonstration

Qualification of materials

Manufacturing process adapted

Empty bag qualification and its shelflife

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# COMPANY OVERVIEW


- Independant Company located in south west of France
- Manufacturer of flexible bags and associated connectors
- 100% dedicated to pharmaceutical market since 1972

# LVP system application diversity

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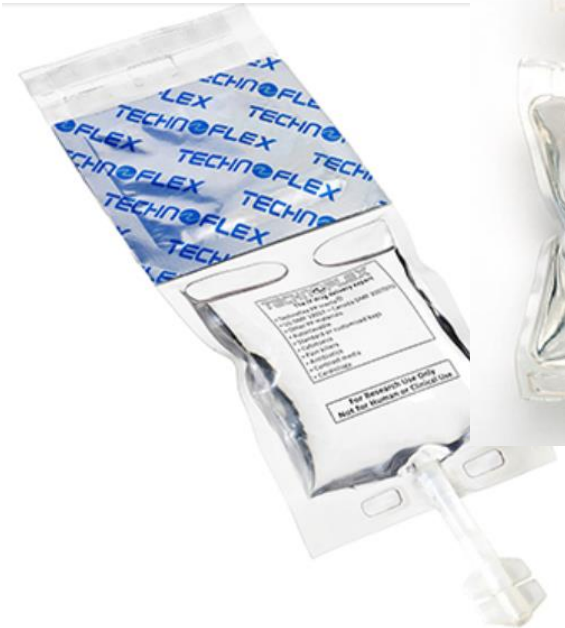
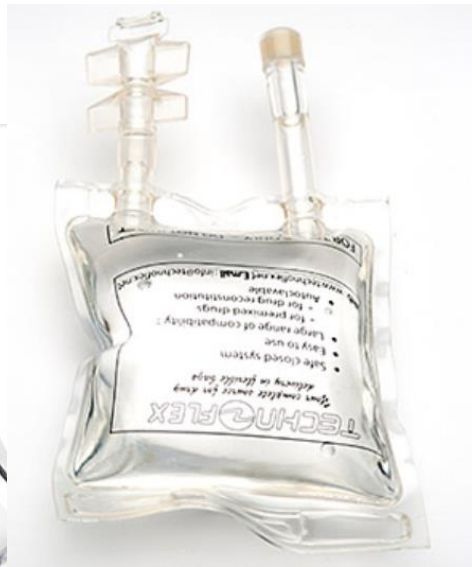
- Will contain different solutions (Fluids, dextrose solutions, electrolytes, drugs, contrast products…)
- Various volumes and size

- Shape adapted to application:
  - Ready to administrate
  - Ready for reconsitution

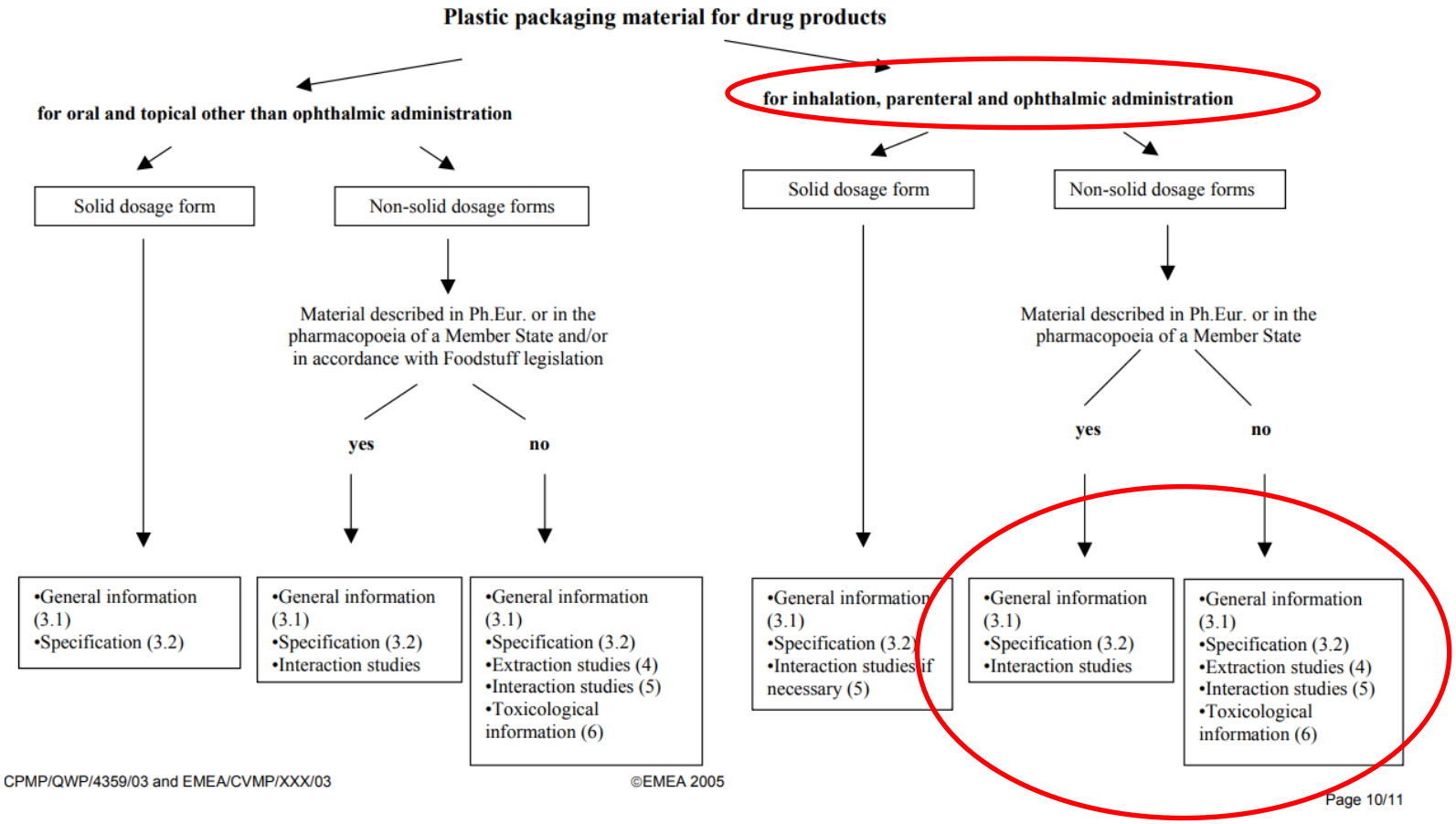



- One or 2 tubes
- One or multi chambers
- Various connectors

# GUIDELINES : EUROPE EMA

European Medicines Agency
*Inspections*

## GUIDELINE ON
## PLASTIC IMMEDIATE PACKAGING MATERIALS




CPMP/QWP/4359/03 and EMEA/CVMP/XXX/03

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FDA U.S. FOOD & DRUG ADMINISTRATION

# Container Closure Systems for Packaging Human Drugs and Biologics

*Guidance for Industry*

| | |
|---|---|
| **Description** | Overall general description of the container closure system, plus:<br><br>For Each Packaging Component:<br>• Name, product code, manufacturer, physical description<br>• Materials of construction (for each: name, manufacturer, product code)<br>• Description of any additional treatments or preparations |
| **Suitability** | Protection: (By each component and/or the container closure system, as appropriate)<br>• Light exposure<br>• Reactive gases (e.g., oxygen)<br>• Moisture permeation<br>• Solvent loss or leakage<br>• Microbial contamination(sterility/container integrity, increased bioburden, microbial limits)<br>• Filth<br>• Other<br><br>Safety: (for each material of construction, as appropriate)<br>• Chemical composition of all plastics, elastomers, adhesives, etc.[a]<br>• Extractables, as appropriate for the material[b]<br>Extraction/toxicological evaluation studies, as appropriate<br>Appropriate USP testing<br>Appropriate reference to the indirect food additive regulations (21 CFR 174-186)<br>• Other studies as appropriate<br><br>Compatibility: (for each component and/or the packaging system, as appropriate)<br>• Component/dosage form interaction, USP methods are typically accepted<br>• May also be addressed in post-approval stability studies<br><br>Performance: (for the assembled packaging system)<br>• Functionality and/or drug delivery, as appropriate |
| **Quality Control** | For Each Packaging Component Received by the Applicant:<br>• Applicant's tests and acceptance criteria[c]<br>• Dimensional (drawing) and performance criteria<br>• Method to monitor consistency in composition, as appropriate<br><br>For Each Packaging Component Provided by the Supplier:<br>• Manufacturer's acceptance criteria for release, as appropriate<br>• Brief description of the manufacturing process |
| **Stability** | • See section III.C.4 |

# Design challenges : combine performance, quality and safety

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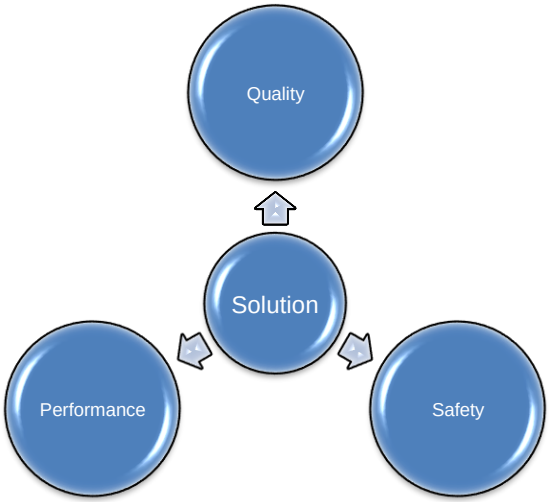
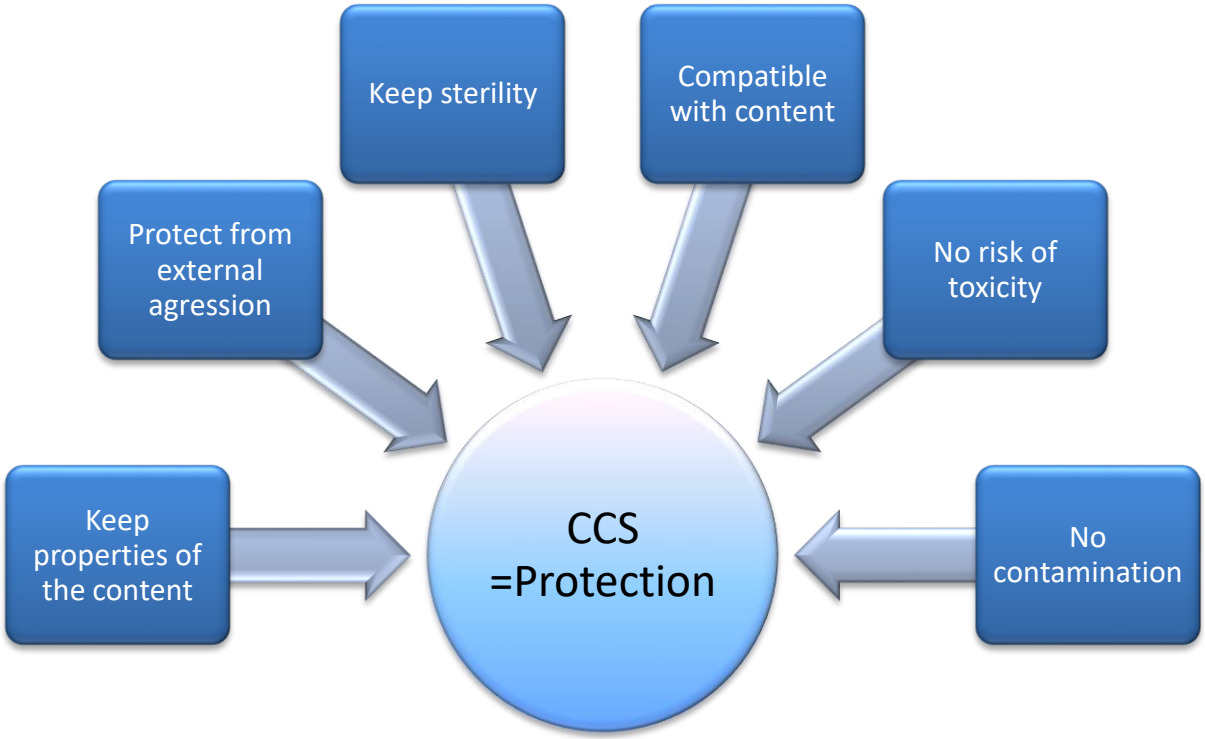



**Adapted to the Intended use**

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# Customer expectations: Conformance demonstration

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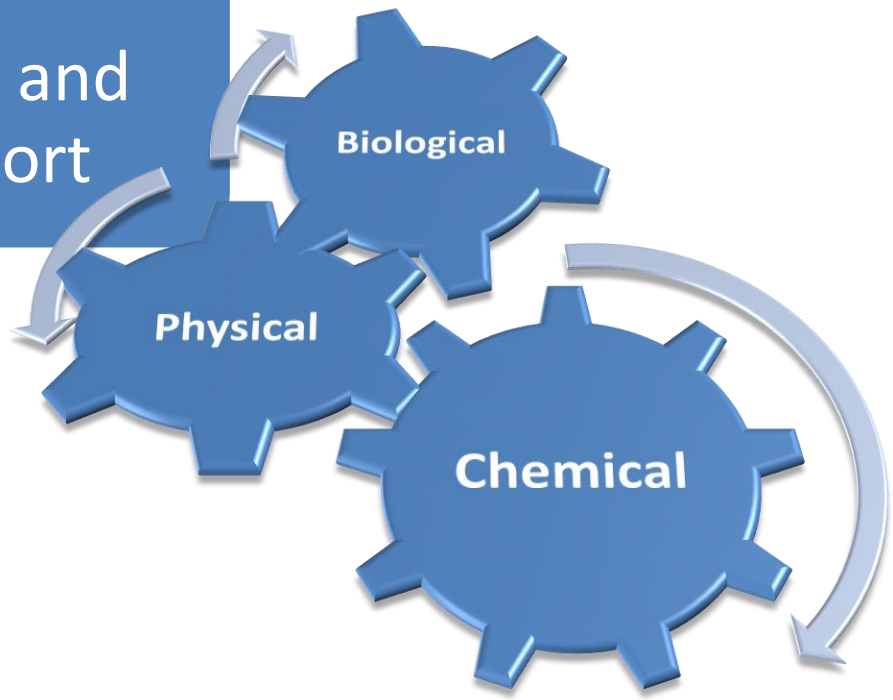
Material and Components

Empty bag

Conformance

Manufacturing and sterilisation process

Storage and transport

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# Qualification of materials

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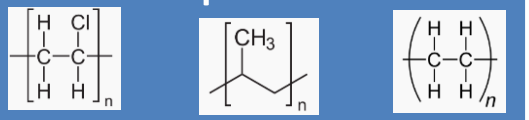
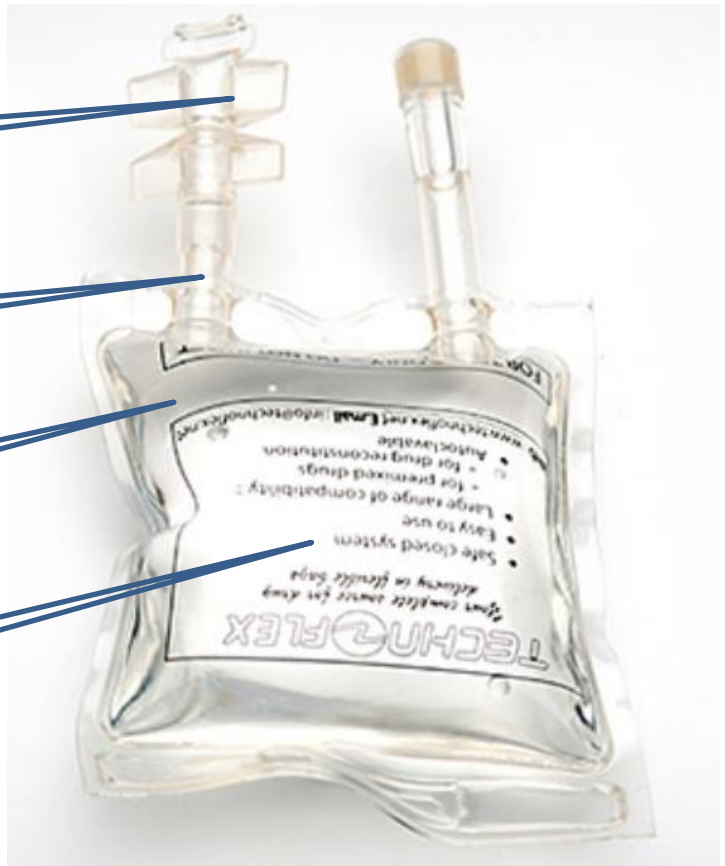
## Material and Components



A bag is composed of

- Twist-off and injection site
- Tubing
- Layflat tubing/film
- Printing film



# Qualification

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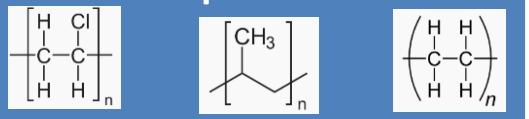
## Material and Components



Material used for LVP are polymers material such as

- Polyethylene (PE)
- Polypropylene (PP)
- Polyvinylchloride (PVC)
- Ethylene vinyl acetate (EVA)

- Combination of some of these materials (multi layers films or coextruded tubing for example) with additives

Pharma grade
Food compliant
REACH compliant

## Qualification of protection properties

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- Physicochemicals properties définition :
  - Barrier properties
  - Ligth transmission measurement
  - Gaz exposure : Oxygen, water vapor, $CO^2$
  - Thickness
  - Resistance : Elongation, breaking characterization
  - Identification (IR spectrum), DSC
  - Chemical characterization according to USP <661-1> and/or EP 3.XX corresponding to material : Acidity/Alcalinity, TOC, Reducing substances, UV absorbance…..

- Chemical testings such as extractable profilling and toxicological assessment of results
  - USP <1663> and/or ISO 10993-19
  - Elemental impurities ICH Q3D

## Qualification of compatibility properties

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- Food compatibility
- Biocompatibility established
    - Citotoxicity , implantation …:ISO 10993 and/or USP <87> and USP <88> conformance (USP CLASS VI)

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# Manufacturing process adapted

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Manufacturing environment needs to be controlled to prevent contamination of bags :
ISO 7 or 8 according to ISO 14644

Manufacturing and sterilisation process

# Sterilisation process

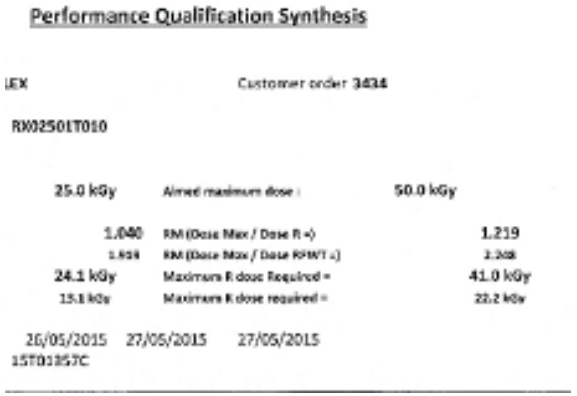
Case of aseptic filling

Gamma or e-beam radiation process

IQ/OQ/PQ according to ISO 11137 standard

Tests performed at different dosis:

- Routine dose
- Maximum dose



Performance Qualification Synthesis

IEX Customer order 3434

RX02501T010

| | | |
|---|---|---|
| 25.0 kGy | Aimed maximum dose : | 50.0 kGy |
| 1.040 | RM (Dose Max / Dose R =) | 1.219 |
| 1.459 | RM (Dose Max / Dose RPMT =) | 2.308 |
| 24.1 kGy | Maximum R dose Required = | 41.0 kGy |
| 15.1 kGy | Maximum R dose required = | 22.2 kGy |

26/05/2015 27/05/2015 27/05/2015

15T01357C

Irradiation → Impact on material

- Reticulation
- Fragility

Manufacturing and sterilisation process

# Empty bag qualification

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The standard followed for finished bag qualification is the ISO 15747:
Plastic containers for intravenous injection

- Physical requirements are mostly mechanical testings:
  - Compatible with sterilisation process: Validation test are performed after sterilization
  - Resistance to temperature, pressure and leaks
  - Resistance to drop
  - Transparency
  - Permeability
  - Contamination by particles
  - Hanging hole strength
  - Printing resistance
  - Spiking conformance
  - Self sealing of injection site

# Empty bag qualification

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- Chemical qualification
  - Acidity/Alcalinity of container (USP 661-2 or EP 3.2.2.1)
  - UV absorbance
  - Metals extractables
  - Residual solvents : ICH Q3C (Ethanol or Cyclohexanone)

- Biological qualification:
  - Cytotoxicity (USP 87)
  - Impermability to microorganisms
  - Endotoxin level (LAL test)

ISO International Organization for Standardization

Empty bag

## Shelflife qualification

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Same tests will be performed after ageing tests

6 months Accelerated ageing : 40°C ± 2°C/75% RH ± 5% RH

Long term natural ageing: Ambient temperature

Shelflife of 3 years

Storage

# And after .....


Change control

From Supplier
From Regulation

Nitrosamines

REACH

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# Thank you for your attention