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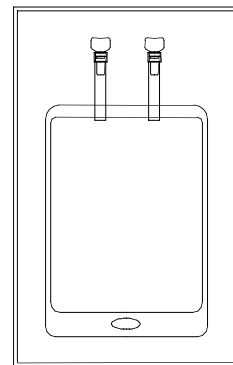
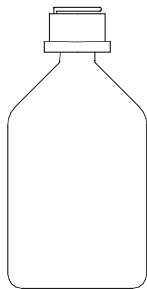
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## Packaging Form Comparison:

### **bottelpack<sup>®</sup> bottle versus Non-PVC-bags**

An integrated evaluation of plastic packaging forms for standard infusion solutions

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**Contents**

- Introduction** ..... 3
- Packaging** ..... 4
  - Products..... 4
  - Requirements ..... 4
  - Forms and formats ..... 4
  - Materials ..... 5
  - Design ..... 6
  - Withdrawal system (Eurocap) ..... 7
  - Outer bag..... 8
  - Comparison of characteristics ..... 9
  - Mechanical load capacity ..... 9
  - Suitability for mixtures ..... 10
  - Pressure infusion..... 10
  - Air intake ..... 11
  - Particles ..... 11
  - Shelf life ..... 12
  - Cardboard box packing ..... 12
  - Recycling ..... 12
  - Application ..... 12
  - Outlook..... 13
  - Packaging form evaluation ..... 13
- Production and installations** ..... 14
  - Production steps ..... 14
  - Automation ..... 15
  - Investment and maintenance ..... 16
  - Personnel requirements ..... 16
  - System efficiency ..... 16
  - Scrap and customer claims ..... 17
  - Production costs..... 17
- Conclusion** ..... 18
- Addendum**..... 19
  - Where bags are applicable ..... 19
  - Where glass bottles are applicable ..... 19

### Introduction

Standard solutions dominate the infusion market. Packaging of solutions need to be safe, cost efficient and user friendly.

Main requirements such as:

- Storage
- Solution extraction
- Injection of additives
- Emergency application

need to be met in a safe and reliable way.

Plastic containers are primarily used worldwide such as:

- PE or PP bottelpack® bottles
- PVC-bags
- Non-PVC-bags

The use of PVC-bags remains very popular in many countries. But due to environmental and medical concerns they have become subject of criticism. Non-PVC-bags are supposed to replace PVC bags in the future.

Following the packaging forms **bottelpack® bottles (BP-bottles)**, which are manufactured based on the BFS-method, are to be compared with the **Non-PVC-bags**, which are manufactured based on the FFS-method and are to be evaluated based on their specific characteristics along with specific production technology.

Evaluation goal: an integrated study of these packaging forms.

## **Packaging**

### **Products**

Both packaging forms are primarily made of polyolefin (PE / PP). The materials' diffusion and adhesion characteristics are of particular importance when used to package infusion solutions.

Polyolefin plastics have a very good water steam barrier, a bad oxygen barrier and very low adhesion capability.

This means that these packaging forms are ideal for watery standard solutions. The plastic walls' low adhesion capability makes the preparation of additive mixtures possible.

Oxygen sensitive products (amino acids, fat solutions) can only be packaged with additional diffusion inhibitors. They have a shorter shelf life and are therefore not really suitable for this type of packaging.

### **Requirements**

All major packaging requirements are outlined in DIN 58363-15 and ISO 15747 (draft).

Long shelf life, even under difficult climatic conditions, a high mechanical load capability, chemical and physical product purity and simple, safe handling of applications are of utmost importance.

In addition it should be possible to perform pressure infusion, and prepare additive mixture preparation etc.

Cost efficiency is of particular importance.

### **Forms and formats**

Container sizes of 100, 250, 500 and 1000 ml are used for the infusion process. 50ml containers are used for mixture preparations. All sizes are available in either packaging form.

Bottles are usually oval shaped or flat shaped. These shapes allow optimization of characteristics and production cost. Bag-like designs are also used.

Bag shapes are right angled with connectors on the small side.

## **Materials**

### BP-bottles

Single layered mono materials of PE or PP are used for the production of bottles. The bottle cap is usually made of the same material, which assures a safe and simple connection.

A well transparent and flexible single unit packaging with good all-round characteristics and wall thicknesses of  $< 300\mu\text{m}$  is produced.

The materials are reasonably priced, extensively tested and always available. Scrap material can be reused in further production processes or used to manufacture bottle caps.

### Bags

To achieve the PVC bags' specific characteristics (transparency, high flexibility, temperature stability, sealing) by using polyolefin, multiple layered foils and several layers of these foils are required. In addition the 3 to 5 individual foil layers consist of compounds of 1 to 3 raw materials each.

Foils can contain up to 10 different raw materials. Foil thickness is kept to under  $200\ \mu\text{m}$  to be cost efficient. This, however, shortens shelf life.

For the production of port systems, additional different plastics are used, which brings the total of primary raw materials to up to 15. In addition a primary coat foil of 1 to 5 additional raw materials is possible and needs to be taken into consideration.

### Evaluation

The rapid progress and change in the plastics market, in particular where high-tech products are concerned, causes intermittent short-term raw material shortages. The probability increases the more raw materials are used. Therefore bag production is primarily affected. To change the pharmaceutical industry's packaging material composition would be very involved, risky and costly.

This complex material situation, coupled with costly production of foils, tubes and port systems create significantly higher material cost for the bag industry, without showing relevant and significant advantages.

## Design

### BP-bottle



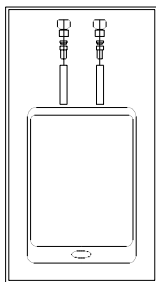
The BP-bottle consists of 3 parts:

- Bottle, produced and sealed
- Cap, premanufactured, with pre-inserted disc of synthetic ungalvanized rubber or TPE (see drawing)

Since the BP-bottle consists of such few parts it provides quite a few advantages such as:

- Few production phases during production process
- High production process and systems safety
- Highly efficient production process
- Low scrap parts
- Few inspection phases
- Low cost

### Bag



Depending on port system the bag consists of up to 10 parts:

- Foil
- 2 connector tubes
- 2 port lower parts
- 2 port upper parts
- 2 separators (septum)
- Outer bag

Bags with port systems, similar to the BP-closure, directly sealed into the foil, consist of 6 or more parts.

The high amount of the bags' components result in the following disadvantages:

- Many phases to produce components and product
- Use of several machine installations needed = resulting in reduced production and systems safety
- Many connection points on final product

- Increased inspection phases required
- Increased scrap material → higher scrap probability
- Reduced product efficiency
- Higher material and production cost

### Evaluation

When a packaging material consists of several components the production process and production phases become more involved and the defective product probability increases.

This happens in particular when joining the separate parts requires complicated technology, which is the case in bag production.

Bag production is clearly more complicated, subject to defects and good quality is more problematic in comparison to the few phased and simpler production of BP-bottles.

This again causes higher bag production cost.

### **Withdrawal system (Eurocap)**

#### BP-bottles

This withdrawal system known as eurocap, is tightly welded to the bottle top separated by a set rubber disk. A tear-off or tear-out part assures sterile protection of puncture area. Puncture point can be positioned in one or 2 separate areas. The rubber disk, located in the closed bottle top, does not come in contact with the solution.

Caps are to DIN 58374 norm (ISO 15759, draft)

#### Bags

Bag-withdrawal systems (ports) vary in basic structure, type, size and application.

Version 1: Similar to BP-cap, i.e. 1 form-stable component with rubber closure, connected directly to the foil or connected by a tube.

Version 2: 2 tubes with plugged in port-parts for withdrawal and injection. These parts are designed according to specific requirements.

Beyond this several varieties can come into play. Bag-ports are not subject to norms.

## Evaluation

Both systems make a safe application possible. The BP-cap is simple to understand, bag ports are more complicated.

## **Outer bag**

Due to the PVC bags' high water steam diffusion, outer bags are needed. To avoid short shelf lives a polyolefin-outer bag became necessary.

## BP-bottles

BP-bottles do not require an outer bag. The use of mono-polyolefin materials and wall thicknesses of <math><300\mu\text{m}</math> provide an excellent water steam barrier, which make a shelf life of up to 5 years possible. In addition the bottles ruggedness and cap shape with sterile tear-off part eliminate the need for an outer bag.

## Bags

Non-PVC-bags require an outer bag for 3 reasons:

- The primary foils' compounds reduce the water steam barrier. The water steam barrier is further reduced due to the thin foil thickness
- Without an outer bag the primary foil can easily be damaged
- Outer bags are needed to protect ports from internal damage and damage to other bags.

In spite of the use of outer bags product shelf life is significantly lower when compared to bottle products.

## Evaluation

Outer bags are costly as far as investment, material and scrap products are concerned, without achieving benefits for the user.

(Exception: additive preparation under sterile conditions)

Defective products increase.

In addition outer bags prevent systematic quality control of bags, such as pinhole checking.

This leads to higher cost without achieving improved quality.

## Comparison of characteristics

According to DIN 58363-15

Characteristics	BP-bottle	bag
Sterilization capability	PE: <115°C, PP 121° C	121° C
Pressure resistance, Impermeability	++	+
Drop resistance	++	+
Transparency	+	++
Water vapour barrier	++	+
Particle contamination	++	++
Cover of closure	++	+ *)
Puncture point, Adhesion strength, Injection point	++	++ *)
Hook	++	+
<b>Other:</b>		
Collapsibility	O	++
Standing capability	++	-
Chemical requirements	++	+ *)
Biological requirements	++	++

\*) various designs are possible

In general both packaging forms meet the standard norms' requirements. Bags have better transparency and are collapsible. BP-bottles' strength can be found in their ruggedness and product protection.

### Mechanical load capacity

Damages and micro leaks of packaging forms threaten application of infusion solutions.

The mechanical stress to the packaging forms during production, storage and especially during transportation, possibly combined with extensive climatic fluctuations can be significant.

BP-bottles have been tested for decades: they can withstand high stress loads with very low risk factors. This is due to their design and production: there is just one component with only 2 seams. The wall is smooth, maintains its shape and has high resistance capability.

Due to the fact that the product consists of many components, bags have a lot of problem areas. Foil weld seams, weld seams to tubes/port systems, plug connectors etc. Foils are usually less resistant to damage. Even the additional outer bag provides little extra protection.

More defective products and more customer claims confirm the existence of these problem areas.

## **Suitability for mixtures**

Preparation of additives in carrier solutions usually takes place in small volume containers and to different methods

- Injection
- Transfer of liquids through adapters
- Dissolution of dry substances through adapters

Requirements to packaging forms vary in regards to air volume and injection volume.

Both packaging forms are suitable to various degrees.

Due to their flexibility, bags have greater injection volume, the air volume, however, is too low.

BP-bottles' solidity presents an advantage especially during the mixing process. The air volume is sufficient to perform all mixing procedures.  
(See: "*Pressure infusion*")

## **Pressure infusion**

Special circumstances (emergency applications) require quick infusion. In this case the container is subjected to up to 0.5 bar excess pressure in a pressure collar. The container has to have sufficient elasticity and needs to be compression proof.

The air volume in the container is of particular importance. Introduction of air bubbles into the patient need to be avoided by all means.

Both packaging forms are suitable for pressure infusion.  
Additional remarks:

### Bags:

Bags collapse almost entirely during withdrawal process, i.e. even the air is moved into the transfer device. The air volume in the container needs to be very low. This works against the requirement for higher air volume for mixing purposes. (Usually with small volume bags).

The variable, uncontrollable air intake in bags during the storage period is of particular concern, a problem associated with pressure infusions.  
(See "*air intake*")

### BP-bottles

Due to their design BP-bottles have a greater air volume. This air volume is needed to fill the non-collapsible areas during withdrawal without air intake. The relatively large air volume does therefore not present a problem during pressure infusion. Little or no air is squeezed from the pressure collar and usually remains in the non-collapsible areas.

## **Air intake**

Gas diffusion through polyolefin is relatively high. This causes an air intake in liquid filled containers, when there is no counter pressure present.

This situation can lead to significantly higher and uneven air volumes after a few months and can therefore create problems.

### Bags

The highly flexible bags do not provide mechanical resistance to air intake, the increase in air is therefore significant. Bags that are stored at the bottom of a carton do not take on air, since the weight of the upper bags prevents intake of air. This can lead to a variety of air volumes in bags stored in one carton and can present a problem during application.

### BP-bottles

The bottles' higher form stability keeps air intake to a minimum. Cardboard box packing is of no consequence.

## **Particles**

Material particles from both packaging types are of no concern. Main source for trace impurities come from primary parts and production processes.

### Bags

There are many possible sources for particles. The many production phases and interim preparation of components are the reason for the many sources for particle contamination.

In addition the critical steps required in bag production create potential particle problems. These are : cutting phases of foils and tubes, plug phases of mandrels and ports etc. Efforts to run particle free production phases are far greater for bags than BP-systems.

### BP-bottles

BP-bottles are produced by a blow-fill-seal method. Possible particle sources are manageable and controllable.

BP-bottles are part of the most particle free packaging forms for infusion solutions. Many years of experience confirm this fact.

## **Shelf life**

Possible shelf life of products for standard solutions depends on water vapour loss of solutions, which is limited to maximum 5%. As mentioned before, bags experience significantly higher water vapour loss and therefore reduced shelf life.

Typical shelf lives:

<u>BP-bottles 500ml</u>	up to 5 years
<u>Bags 500 ml (incl. outer bag)</u>	up to 3 years

## **Cardboard box packing**

The cardboard boxes need to protect the containers and allow safe storage and shipping. Requirements for each packing form differ greatly.

### BP-bottles

A high mechanical ruggedness and stability require average cardboard boxes. Standard collapsible cardboard boxes at low cost are definitely adequate.

### Bags

Very sophisticated cardboard boxes are required to properly package bags:

- No inside edges because of possible damage to bags
- Stacking difficulties

Costly cardboard box design and paper quality lead to significantly higher packing expenses.

## **Recycling**

Only packaging forms produced from one material can be recycled. That means BP-bottles can be recycled, and bags cannot be recycled.

The relevance of this point depends on recycling methods and national ordinances. This has to be evaluated on an individual basis.

## **Application**

The major difference between packaging types are the outer bag and flexibility.

Removal of outer bag requires additional handling and creates additional waste. Both types need to have the puncture cover removed.

## Bags

The bags ability to easily collapse allows airless withdrawal. Once collapsed it is difficult to read the remaining content on the scale.

The remaining contents can amount to up to 10ml. Two tube bags always retain some liquid in their tube and port fill areas. This variable is difficult to handle when small amounts need to be injected during application.

## BP-bottles

The air intake through the infusion system achieves a steady flow and assures entire emptying of bottle. This is really of no consequence since parallel to the use of BP-bottles the use of glass bottles with standard air intake is standard procedure worldwide. Quantitative determination is therefore exact and remaining contents <2ml.

## **Outlook**

What progress can be expected, what is necessary?

## BP-bottle

Changes to this reliable product can only be expected in regard to possible new plastic material and continued effort to optimize design details.

There are no immediate changes required.

## Bags

The primary foils and production technology underwent the most intensive development. Quality and processing need to be improved and production cost significantly lowered. A reduction in cost can hardly be expected due to the present existing bag designs. New bag systems are not expected to be available in the near future.

## **Packaging form evaluation**

**PVC-bags** are a (war) product from the fifties. Top priority was to have an unbreakable product.

**Non-PVC-bags** are actually just a copy of PVC bags but made of different materials. Therein lies the problem: cost, characteristics and mechanical quality of PVC-foils cannot (yet) be obtained with the use of polyolefin material.

The first BP-bottles appeared on the market in the seventies. Several integrated production steps limit the process to produce one shape and few individual components, which keep production cost low.

Three criteria are compared : Application, quality and cost.

### Application

Both packaging forms meet all requirements. The higher flexibility of bags is significant. This is the major difference between bags and bottles. This flexibility can sometimes be advantageous, but can also be a disadvantage since it makes handling complicated.

### Quality

In almost all aspects the BP-bottles quality is better when compared to the bags. (Mechanical load, shelf life, air diffusion, outer bag etc.)

### Cost

Production of bags is, without exception, significantly more costly when compared to BP-bottles. Material cost for bags are 50 to 100% higher than those of bottles.

500 ml BP-bottles : 0.09 Euro material costs  
500 ml bags: 0.16 Euro material costs (real examples)

### Conclusion

There are no valid reasons to switch to Non-PVC-bags for standard solutions. Taking the cost situation into consideration, the use of bags does not make sense.

## **Production and installations**

### **Production steps**

The amount of production steps from start to the finished product differ significantly in the production of the two different packaging forms. The product's many components, their production and assembly, make this production process very different. Separate production runs for auxiliary components need also be taken into consideration.

### BP-bottles

Bottles are produced directly from extruded granulates. Blow, fill and sealing take place in the same blow mould. This reduces handling and positioning complications. Subsequent to flash removal the cap is then welded to the bottle in one additional step.

Following the sterilization process packing steps (quality control, identification marking, packing) take place on a standard installation.

The single part cap is formed externally, the rubber disk is placed in the cap (alternate 2-K method).

### Bags

The production of bags requires a multitude of interwoven production processes, due to the far higher amount of individual components. Between production processes, transfer and positioning phases are required. Product quality and accuracy depend on high caliber production steps.

Cutting of foils and tubes, sealing of foils and connector parts, various plug phases, all these varied steps are critical and influence the quality of product.

Sterilization, outer bagging and packing require sometimes special equipment. Quality control and packing are performed semi-manually (due to the bags flexibility as well as the outer bag).

External foil production for primary bags and outer bags, tube extrusion forming and applying of connector parts as well as rubber disks are required. This is very costly.

### **Automation**

Whenever automation of production of each packaging form is being evaluated one runs into significant differences with extensive consequences.

### BP-bottles

Bottle production with cap welding is usually a fully automated process. Sterilization and/or drying and all packing processes up to palletizing can be performed on automated standard machines. Quality control to check for visual defects and micro leaks can also be performed on tested fully automated systems.

### Bags

The production of bags requires many steps. Automation of this production process (bag production, outer bagging and sterilization) is very complex. Because of the outer bag, the quality control phase where the product is checked for leaks (which are more frequent due to the higher defect probability and therefore of major concern), cannot (yet) be automated. Since the handling of flexible bags is more intricate, the packing process needs to be performed manually.

## **Investment and maintenance**

It is almost impossible to determine a flat rate expenditure amount. In addition to the actual product cost, cost for the production of auxiliary components need to be considered. There are numerous and intricate components.

This also applies to the entire handling process. Similar automation and output require higher expenditures where the production of bags is concerned.

In addition, maintenance cost for bag production installations are higher, due to the many production steps, complex production stations and scrap parts.

## **Personnel requirements**

### BP-bottles

BP-bottle production installations can be run with a minimum of personnel. Automated systems where 3.600 bottles per hour are manufactured (starting with the granulates to end product palletizing) need only 3 workers.

### Bags

Personnel requirements for existing bag production are much higher: little automation is possible there is higher defect probability in production processes and higher quality control involvement.

This requires two to three times more personnel for bag production when compared to the comparable BP-bottle production.

## **System efficiency**

### BP-bottles

Many years of experience show, that these BP-systems and all production steps are to over 95% efficient.

### Bags

Available data from the few existing bag manufacturers worldwide show a significant lower efficiency. The numerous production steps cause a reduced total efficiency.

Rarely more than 80% efficiency is being achieved, usually much less.

## **Scrap and customer claims**

The pharmaceutical production's scrap portion tells you a lot about the safety and stability of their specific production process. Exceeding scrap limits (i.e. 2%) usually require to repeat the cost intensive quality control of produced products. Manual inspection detects only about 90% of defective products.

The amount of scrap products is in direct relationship to customer claims, due to many weak areas and not detected errors.

Naturally the type of scrap (scrap can be a serious problem or of little consequence), and the probability for scrap is important.

### BP-bottles

Many years of experience show, that there is a constant scrap rate of below 1% where BP-bottles are concerned. The fully automated quality control achieves an above average high defect detection.

Subsequent quality control steps are not required; customer claims about BP-bottle are very low .

### Bags

Due to the numerous product components, assembly processes and welded areas, higher scrap parts are the result. This usually causes scrap rates of over 2% many times even higher.

In addition to the loss of products, there are higher additional quality control costs and product safety sinks.

This leads to significantly higher claims from customers where bags (also PVC) are concerned, when compared to customer claims in connection with bottle packaging.

## **Production costs**

Production costs depend on individual situations and additional conditions. It is therefore not possible to estimate general production costs.

Production costs for BP-bottles can be obtained from various production sites, are verifiable and are retraceable.

Due to fewer existing bag production manufacturers it is more difficult to arrive at production costs. Fewer data is available, especially as far as additional cost factors such as repeat quality control costs, are concerned.

High performance production costs for 500 ml containers produced in an automated system can be:

BP-bottles:           0.35 Euro

Bags:                   0.60 Euro

The amount listed for BP-bottles are upper cost limit, those for bags lower cost limit.

Due to presently available technology and materials an appreciable production cost reduction for bag production cannot be expected.

## **Conclusion**

All production phases for Non-PVC bags are more involved, more difficult and more costly when compared to the production of BP-bottles. This includes material cost, production cost and ends with packing.

The high flexibility of bags is very advantageous (but can also be a disadvantage); in addition the somewhat better transparency is of advantage. However, the list of disadvantages for bag production is much longer when compared to the bottle production's list of disadvantages.

The practicality of bags to today's technology for standard solutions to 1000 ml is definitely questionable.

In comparison, the BP-bottles meet all requirements such as high quality combined with low cost. This is a verifiable fact obtained from numerous production site data and markets.

## **Addendum**

### **Where bags are applicable**

Certain medical solutions require characteristics, which can no longer be met by bottles and similar packaging forms. These are:

- Large volumes of 2000 to 5000 ml (<5000 ml use of canisters)
- Special hook-up and connection systems (i.e. dialysis)
- Multiple chamber packaging with mixing attachment
- Solid-liquid-packaging (multiple compounds)

These requirements are met by bag packaging and their application in these situations is ideal.

### **Where glass bottles are applicable**

Glass bottles are heavy, subject to breaking and their production energy intensive. Their special advantage lies in their diffusion impermeability; their reaction incapability, very high temperature stability and bottles can be entirely recycled.

Glass bottles are ideal for oxygen sensitive products such as amino acids, fat solutions etc. They have a long shelf life. High temperature stability and safe processability make bottles ideal for aseptic filling ( pre-sterilization at < 300°C).

Certain bottles can be used for multiple purposes.

Glass bottles are not suitable for standard solutions due to their high weight, high transportation costs and high packing requirements.

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