PRIMARY PACKAGING

The art of innovation

free*flex*®

Technical manual

Fresenius Kabi
Caring for Life

Fresenius Kabi Deutschland GmbH
Else-Kröner-Str. 1
61352 Bad Homburg v.d.H., Germany
Tel.: ++49 (0)61 72-686-73 09
Fax: ++49 (0)61 72-686-81 86

Fresenius Kabi
Caring for Life

freeflex®

The innovative container in infusion therapy

Contents

page

Innovation driven by experience in container technology

Fresenius Kabi has a broad competence in flexible container technology for infusion and clinical nutrition therapy. Eight years after the introduction of the first flexible infusion container by Fresenius Kabi, the 3rd generation of freeflex® containers is available. The development of this new generation is based on Fresenius Kabi's broad experience and understanding of the technology. In anticipation of current and future customer needs this was the base for new innovations to further improve handling and safety. Four patents were realized in the new freeflex® technology underlining the level of innovation of this container.

freeflex® anticipates the evolution of infusion techniques.

Infusion therapy is becoming an increasingly complex and challenging area of medicine mainly because of the need for heightened safety, specialisation of infusion protocols (antibiotic therapy, chemotherapy, etc.) and the introduction of new drugs with complex handling protocols and stability issues. The features of the container play an important and constantly increasing role in fulfilling these requirements.

The improvements in the 3rd generation of freeflex® address these current and future requirements.

Today, three different types of large volume I.V. containers are available:

- **GLASS BOTTLES:** They have well-recognised properties, like being environmentally friendly, inert and a good barrier, but are disadvantaged by being heavy, not collapsible and having breakage hazards. In addition, energy consumption for production, recycling and transport exceeds non-glass alternatives.
- **PLASTIC BOTTLES**: They are usually made of PE or PP. These enhance the glass by being lighter in weight and less fragile. Bottles are available in different presentations, with a single port or recently also with separated ports.

These two containers are rigid and consequently require germ-free air ingress to allow outflow. The infusion system is therefore open and at risk of contamination. In addition, pressure infusion (e.g. in emgerency care) is not possible with rigid containers.

- **FLEXIBLE PLASTIC BAGS:** They are available in PVC and PVC-free variations. They offer one or two separate ports, low weight, reduced waste volume and full collapsibility (closed system infusion). First ones have compatibility limitation with some IV drugs, plasticiser problems and environmental issues. PVC-free bags are the first choice when safety and handling become the key selection criteria.

Fresenius Kabi has responded to these challenges with a new concept in infusion therapy systems. freeflex® is benefited from significant improvements in infusion containers technology. It reaches the drug compatibility standard similar to glass, exceeds glass in ecological aspects and retains the well accepted characteristics of an infusion bag: clarity, flexibility, low weight and separate ports for injection and infusion.

freeflex® advantages

freeflex® is a PVC-free flexible container for different types of I.V. solutions. Its benefits arise from its PVC-free materials, the patented ship shape port technology and the innovative product concept (consisting of material, bag design, port technology and overwrap):

Advantages of the materials used in freeflex® are:

Free of PVC, plasticisers, adhesives or latex. No migration of additives from foil or ship shape ports into the solution.

Compatibility comparable to glass with the most commonly used I.V. drugs.

Economical and non-polluting disposal.

New container concept freeflex® offers a strictly closed system for drug reconstitution.

Its handling is intuitive, safe and simple, ensures maximum asepsis. (1), (2), (3)

Drug reconstitution with freeflex® transfer device

freeflex® is specially designed to optimise the drug reconstitution process. The unique freeflex® transfer device offers:

- Easy and intuitive handling
- Operator safety
- Maximum asepsis

The injection port is easy to identify by the directional arrows and white colour. As an additional safety measure, the freeflex® transfer device will not fit onto the infusion port.

Avoiding the use of syringes reduces the risk of needle stick injuries. The design of the injection port and transfer device ensures a closed system. This protects the user from chemical contamination and the patient from microbiological contamination

Advantages of freeflex® can be summarized as:

3E
asy handling
nhanced safety
xcellent drug compatibility

+ high ecological standard

Primary container

All components of freeflex® (film, ports and overwrap) are made from PVC-free materials without plasticisers, adhesives or latex. The studies performed with the I.V. drugs most commonly used in hospitals and intensive care units show excellent compatibility.

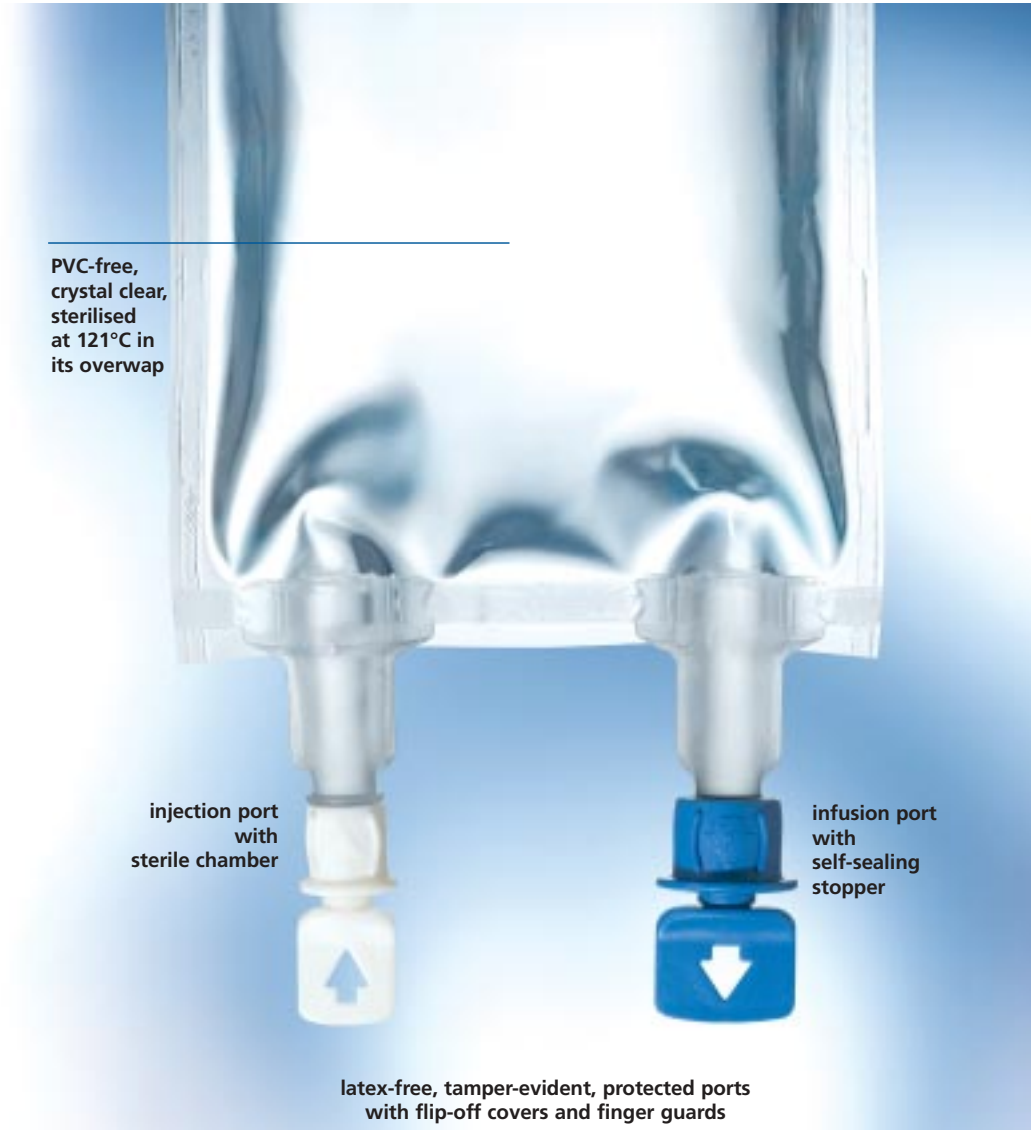
freeflex® is sterilised at 121°C in its overwrap to ensure maximum internal and external asepsis of the primary bag.

This bag has been developed, designed and tested to meet all of the physical and mechanical requirements of the third edition of European Pharmacopoeia "plastic containers for aqueous solutions in parenteral infusion" and the additional specifications of the German norm DIN 58363.

The shape is optimised for both strength and convenience with soft edges that will not cut hands or gloves. The film is crystal clear for easy inspection. The central hanging perforation resists tearing.

Primary container advantages at a glance:

Fact	Advantage	Benefits
PVC Free	No incompatibility with certain drugs, no adsorption of the drug at the inner bag surface, no migration of plasticisers	Excellent drug compatibility
	Does not release dioxin compounds, only CO_2 and H_2O in thermal recycling	Environmentally friendly
No Additives	No migration of additives	Excellent drug compatibility
Sterilised in the overwrap foil at 121°C	No risk of contamination, primary package stays aseptic until overwrap is opened	Patient safety
Optimised bag shape	Easy and safe handling	Patient and users safety
Crystal clear film	Allows easy inspection of the solution and in case of drug reconstitution, monitoring of complete solution of the solvent	Patient safety



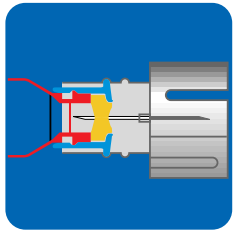
Ship shape port system

freeflex® has separate injection and infusion ports – designed for safe and easy handling. Both ports are made of polypropylene and are therefore PVC and latex-free. For maximum safety ship shape ports are pre-sterilized before being built into the primary bag. Therefore the membranes below the break-off covers are sterile and disinfection before use is not necessary.

By virtue of their arrow and colour coding, the ports are easy to identify and are protected from external contamination by tamper-evident flip-off covers.

Characteristics of each port:

Injection port

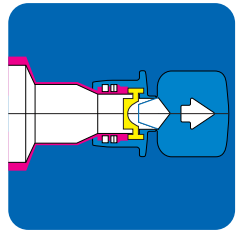


- Convenient port with finger grip for easy handling
- White break-off cover which is tamper-evident, protects the sterile membrane
- Arrow indicates the direction of flow
- Latex-free septum
- Sterile chamber between the latex-free septum and an additional membrane

Design of the injection port allows safe and easy transfer of drugs with syringes and vials.

The injection port is specially designed to dock with the two-stage guides on the freeflex® transfer device. The freeflex® IV container is also compatible with Monovial or Biodome drug transfer systems. Their combined use offers very simple handling to maintain a strictly air closed system between solution and drug during reconstitution. This ensures optimal safety and simplicity.

Infusion port



- Convenient port with finger guard for easy handling
- Blue break-off cover
- Arrow indicates the direction of flow
- Self-sealing, latex-free stopper prevents unintentional leakages after removal of the infusion (I.V.) set

The infusion port has been shown in tests to be compatible with all I.V. sets commonly available in the market.

Ship shape port technology advantages at a glance:

Fact	Advantage	Benefits
Break-off covers as tamper-evident	Ready to use after removal, ensures sterility of the membranes, no contamintation, no disinfection step necessary before use	Patient safety, increased efficiency, easy handling
Different colours and arrow symbols for infusion and injection port	Self-explanatory differentiation of ports and easy to distinguish	Patient safety, easy handling
Sterile chamber in the injection port	Protection against contamination	Patient safety
Self-sealing stopper	Membrane closes if infusion set is removed	No contamination, no accidental loss of solution
Latex-free septum	No risk of latex-induced allergy	Patient safety, no limitations in usage
Semi-rigid corpus	Easier handling even under difficult conditions like Laminar Flow. Better sealing during production	Easy and safe handling

Overwrap

The PVC-free overwrap is peelable, easy to open by using the pre-cut corner stub, and adheres slightly to the primary bag to improve handling even when wearing disposable gloves. The overwrap effectively avoids solution losses through vaporing, even with small bags with an unfavourable volume/surface relation.

While being opened the overwrap does not tear and can act as a possible sterile surface for preparing the infusion system (e.g. in emergency ambulance or at the ward). The overwrap also has excellent clarity to allow visual inspection.

The freeflex® primary bag is internally and externally sterile and can be displayed and used in a totally aseptic way.

PVC-free materials

Bag consists of multilayer film based on polyolefin (PP). Inner layer is polypropylene.

All freeflex® components are made from PVC-free materials.

The primary bag and overwrap film are made by co-extruding several polyolefine layers. Polyolefines are polymers made exclusively from hydrogen and carbon atoms. They are manufactured by the polymerisation of ethylene and propylene, or by the co-polymerisation of these two monomers. Their physical properties are conferred by the three-dimensional configuration of the atoms in the polymer, and not by the use of plasticisers.

This is a fundamental difference compared to PVC, where very high levels of phthalates are used to soften the material.

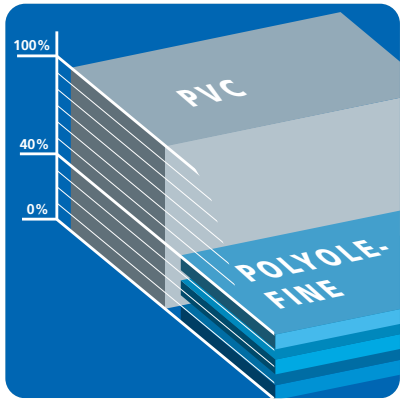
The freeflex® film's performance as a barrier to the migration of water vapour is superior to PVC and guarantees excellent homogeneity of the solution during the shelf life.

The molecular composition of the freeflex® film ensures very low levels of adsorption and absorption of commonly used I.V. drugs.

Ecology

freeflex® has been carefully designed to minimise its impact on our environment throughout its life cycle.

- Manufacturing is phthalate-free and the system is inert during use. (1), (2), (3), (8), (9), (10)
- The freeflex® film contains 60% less material than a comparable PVC bag, saving valuable raw material during the production process and reducing waste.



- By using materials from only one polymer class (polyolefines), recycling is made possible.
- Alternatively, disposal by incineration produces carbon dioxide and water only. Neither hydrochloric acid nor nitrous acids, dioxins or furans are generated. The energy released upon incineration can be recovered for heating.

Shelf life and other characteristics

Sizes and packaging quantities

freeflex® is available in the following sizes and packaged quantities:

50 ml bags:	60 bags per box 32 boxes per pallet	= 1920 bags per pallet
100 ml bags:	50 bags per box 32 boxes per pallet	= 1600 bags per pallet
250 ml bags:	30 bags per box 32 boxes per pallet	= 960 bags per pallet
500 ml bags:	20 bags per box 32 boxes per pallet	= 640 bags per pallet
1L bags:	10 bags per box 32 boxes per pallet	= 320 bags per pallet

freeflex® packaging is optimised for easy transportation, storage in hospital pharmacies and disposal:

The boxes have the same dimensions for all bag sizes, weigh not more than 12 kg when filled, have pre-cut handles on two sides and a pre-cut opening on the side of the box for easy access. The box label is located on this side.

Fill volumes and filling tolerances

50 ml bags:	52.4 to 54.0 ml	500 ml bags:	515.0 to 520.0 ml
100 ml bags:	105.0 to 107.0 ml	1000 ml bags:	1020.0 to 1030.0 ml
250 ml bags:	262.5 to 265.0 ml		

Additional volumes

freeflex® bags can accept without significant overpressure the additional solution volumes as shown below:

Bag size	Additional volume of solution can be added (without pressure)	Total capacity
50 ml	+ 70 ml	+ 120 ml
100 ml	+ 48 ml	+ 148 ml
250 ml	+ 75 ml	+ 325 ml
500 ml	+ 150 ml	+ 650 ml
1000 ml	+ 150 ml	+ 1150 ml

Use of hydrogen peroxide or peracetic acid to sterilise the outer surface of bags in clean rooms or isolators

Tests have been performed on freeflex® and PVC bags containing sodium chloride solution. Bag sizes 50 ml, 100 ml and 250 ml were tested by subjecting them to a hydrogen peroxide or peracetic acid sterilisation cycle typical of that used prior to aseptic compounding. The polyolefine freeflex® bags present a significantly better barrier to these sterilising agents than PVC bags. The use of hydrogen peroxide is recommended because it exhibits even lower migration than peracetic acid.

Resistance in pressure cuffs

freeflex® has been designed to resist the following pressures in pressure cuffs:

50, 100 and 250 ml bags:	300 mm Hg over 3 days or up to one hour at 350 – 400 mm Hg
500 and 1000 ml bags:	300 mm Hg over 7 days or up to one hour at 350 – 400 mm Hg

Accessories for freeflex®

freeflex® transfer device
Offers safety in transferring drugs from the smallest medicine vials, has two-stage locking mechanism.

freeflex® cap
To mark the compounded solutions/ drugs added in the freeflex® bag.

Stability when frozen or heated in microwave

freeflex® can be frozen down to - 22°C or heated in a microwave or hot cabinet to + 37°C without any influence on the physical stability of the bag. This allows the reconstituted drugs a longer shelf life. (3), (4), (5), (6), (7), (8), (9)

Shelf life

The freeflex® material offers a greater water vapour barrier than PVC and has no effect on the pH of the solution.

50, 100 and 250 ml bags:	2-year shelf life
500 and 1000 ml bags:	3-year shelf life

Production process

The primary polyolefine foil used in the bag is manufactured by co-extrusion of different resins. The 3rd generation of freeflex® is produced at three different production sites with the competence centre in Friedberg, Germany. The bags are produced at state-of-the-art automated production lines. All production steps (bag production, filling, overwraping, sterilisation, packaging) are carried out in single interruption free process under clean room conditions.

- The film is laid flat and printed with a label, including variable data like expiry date and batch number.
- It is then cut into lengths appropriate to the bags' size and opened at one end to allow insertion of the ship shape ports and seamed by hot welding. In-line temperature monitoring ensures full control of the critical welding process.

- The empty bag is closed, first with the ship shape injection break-off ports.
- Bags are transferred to the filling area, evacuated, closed with sterile filtered air and filled with solution from holding tanks.
- Filled bags are then closed by plugging the break-off infusion parts onto the ship shape parts and transported to the over-wrapping machine.

- After over-wrapping, the bags leave the clean room and enter the autoclave.
- The sterilised bags are then dried and transferred to the packaging area to be packed in cardboard boxes.

Quality control

Film and ship shape ports

During production of the film in a purpose built clean room, multiple online inspections guarantee the highest possible quality of the entire process. The film thickness and width are measured automatically and continuously. Particles are monitored by an optical inspection system.

Ports

The ports are injection-moulded and pre assembled in a clean room. The pre-assembled ports are sterilised by steam prior to use in the production process to guarantee the sterility of the inner chamber and all surfaces that can be accessible to the final user after removal of the tamper-evident break-off caps. Finished ports are inspected for particles, microbiological contamination, dimensions, functions, tightness and colour.

Infusion solution preparation

After preparation of the solution in stainless steel mixing tanks, a first analytical control checks that the solution is within chemical specifications. The solution is then sterile-filtered to a filling tank. Microbiological and chemical in-process quality controls are performed during the filling process.

Filling and closing

Immediately prior to filling, the solution is pumped through a 0.2 µm sterile filter. In-process physical control checks the print, the air bubble volume, the solution volume, the hanger and the mechanical strength of the bag on a regular random sampling basis.

Over-wrapping, sterilisation and packing

The over-wrapping process is controlled by both the temperature of the welding electrode and the vacuum within the pouch.

Continuous temperature and pressure measurement ensures that each autoclave cycle conforms to the validated sterilisation process.

At the packing stage, an optical inspection confirms:

- The bag print is correct and fully legible
- There are no visible particles contaminating the solution
- The overwrap pouch is correctly positioned

An automatic weight check confirms the correct quantity of bags in each carton.

Quality control samples are finally taken from each batch to perform the chemical, microbiological and physical tests required for batch release.

Maximum safety and highest quality

The overall quality control philosophy of the freeflex® production line is integrated into each single production step and fully documented.

Each tool and production process has been developed, tested and validated to guarantee maximum safety and complete asepsis of the solution and of all components of the bags, the intermediate space between the primary bag and the overwrap, and the internal and external surfaces of tubes and ports.

Instructions for use

freeflex® bag, freeflex® transfer device and freeflex® cap
(These instructions are only intended as guidelines for product use.)

General preparation

- Check the solution composition, lot number and expiry date.
- Inspect the container for damage or solution leakage. If damaged, do not use!

- Using the corner tabs, remove the freeflex® from the overwrap immediately before use.

Infusion

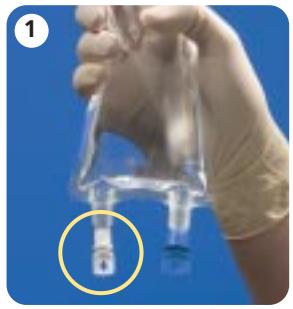
- Identify the blue infusion port.

- Break off the blue tamper-evident cover from the freeflex® infusion port.
- Membrane below cover is sterile – disinfection of the membrane is not necessary!

- Close roller clamp. Insert the spike until the blue plastic collar of the port meets the shoulder of the spike.
- Use a non-vented set or close the air inlet.

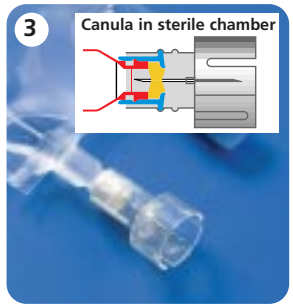
- Hang the bag on the infusion stand. Press drip chamber to get fluid level. Prime infusion set. Connect and adjust flow rate.

Reconstitution with the freeflex® transfer device



- See step 1 from infusion instruction. Use opening aid to remove overwrap. Identify the white injection port.

- Break off the white tamper-evident cover from the freeflex® injection port.



- Push the narrow end of the freeflex® transfer device over the white injection port to the first notch. The tip of the needle is now in the sterile chamber, protected from airborne contamination.

- Prepare the medication vial and connect it to the open end of the freeflex® transfer device. As the opposite end of the freeflex® transfer device needle is in the sterile chamber there is no risk of contamination by ambient air or of drug escape.

- Push the freeflex transfer device with the vial towards the bag to pierce the inner membrane. Press solution into the vial and dissolve the powder.

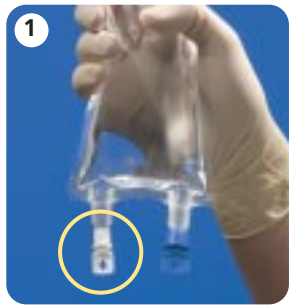
- Turn the vial upside down and press air into the vial to transfer the solution from the vial into the bag. Repeat until all liquid is transferred.

- Mark the injection port with a red cap to indicate that the bag is filled with a drug and attach the label with detailed information to the bag.

8–11

Please follow steps 1–4 under infusion application.

Drug preparation with a syringe



- See step 1 from infusion instruction. Use opening aid to remove overwrap. Identify the white injection port.

- Break off the white tamper-evident cover from the freeflex® injection port.

- Transfer drug from the syringe into the freeflex® bag.
- Use 18–23 Gauge needles

- Mark the injection port with a red cap to indicate that the bag is filled with a drug and attach the label with detailed information to the bag.

5 – 8

Please follow steps 1 – 4 under infusion application.

General protocol

1. Source of active drug

It was decided to use brand products on the European market or products with the same composition as the market leader for the stability tests.

2. Concentration

Based on our experience with stability testing of the products, we know if the degradation of the drug is dependent on the concentration or not. If there is a dependence, we prepare a less stable concentration. If not, we investigate a concentration which is a commonly used dosage for children and adults.

3. Solvent

In general we specified sodium chloride 0.9% in our test protocol because it is the principal solvent in clinical application.

In the event where manufacturer has recommended another carrier solution we used the recommended one.

4. General test parameters

If the formulation of the drug to be analysed is a solution for injection, the specified amount of the drug was injected under aseptic conditions into the filled freeflex® bags.

In the case of a sterile powder for injection, 10 ml carrier solution was removed under aseptic conditions from a freeflex® bag. The drug was dissolved in this amount of solvent and the clear solution was re-injected into the freeflex® bag.

The bags were stored in the dark under the following conditions:

- at room temperature and
- at 2°C – 8°C

An equilibration time of six hours was added to each storage period to simulate the warming of the solution to room temperature before infusion.

According to the Ph. Eur. III, the following parameters were verified:

UV-absorption	(single determination)
pH-value	(double determination)
Particulate matter	(six-fold determination)
Appearance	(three-fold determination)

Methods

1. UV-absorption

The determination was performed by an UV/VIS-double-beam spectrophotometer (Hitachi U-2000), corresponding to the Ph. Eur. III, 2.2.25. A 40 mm glass cuvette was used. The total spectral range (200 – 800 nm) was measured. If no irregular value was detected, only the measured value at 400 nm was reported. The measurement was carried out against water as reference solution.

2. pH-value

The determination of the pH was carried out using a pH meter (WTW 537), corresponding to the Ph. Eur. III, 2.2.3.

3. Particulate matter

The examination corresponds to the USP 23/NF 18 <788> and was executed with the particle-counter model 4100 (HIAC-ROYCO). The quantity of particles ≥ 10 µm/ml and ≥ 25 µm/ml was determined. The solution meets the requirements of the test if the average number of particles present in the units tested do not exceed the appropriate value of 60 counts/ml ≥ 10 µm and 6 counts/ml ≥ 25 µm.

4. Appearance

The visual examination is to be considered as a supplement to the physical investigations performed. The tests were executed with regard to opalescence/opacity, precipitation and gas bubble generation. Any discolouration was also documented.

5. Assays

The contents of the drugs were measured with validated methods by multiple analysis. The freeflex® samples and the control containers (glass bottles) were determined four times at each time point. The results are represented by average values and percentages of the starting concentration. The 0-value of the measurement is equal to 100%. If the loss of concentration during the examination period is less than 10%, the solution can be considered as stable, provided the breakdown products are not known to be toxic.

List of drugs compatible with freeflex® bags

ANTI-INFECTIVES

Acyclovir	Clindamycin
Amikacin	Erythromycin
Amoxicillin	Flucloxacillin
Ampicillin	Ganciclovir
Aztreonam	Gentamicin
Benzylpenicillin	Imepenem-Cilastatin
Cefazolin	Meropenem
Cefotaxime	Mezlocillin
Cefotiam	Ofloxacin
Ceftazidime	Piperacillin
Ceftriaxone	Trimethroprim-Sulfamethoxazole
Cefuroxime	Vancomycin
Ciprofloxacin	

CYTOSTATICS

Carboplatin	Fluorouracil
Carmustine	Gemcitabine
Cisplatin	Ifosamide
Cyclophosphamide	Methotrexate
Docetaxel	Mitoxantrone
Doxorubicin	Oxaliplatin
Epirubicin	Paclitaxe
Etoposide	Vinorelbine

OTHER I.V. DRUGS

Bupivacaïne	Dobutamine
Bupivacaïne - Fentanyl	Fentanyl
Caliciumfolinat	Heparin
Diazepam	

(1) DOOREN VAN AA:

"PVC as pharmaceutical packaging material"
A literature survey with special emphasis on plasticized PVC bags.
Pharmaceutisch weekblad Scientific edition 13, 109-118, 1991.

(2) KOWALUK EA, ROBERTS MS, BLACKBURN HD, POLACK AP:

"Interaction between drugs and polyvinyl chloride infusion bags".
American Journal of Hospital Pharmacy 38, 1308-1314, 1981

(3) PETTY C, CUNNINGHAM NL, MAJOR MC:

Insulin adsorption by glass bottles, polyvinylchloride infusion containers and intravenous tubing.
Anaesthesiology 40, 400-404, 1974

(3) FRESENIUS KABI

"Evaluation of potential migration of traces of hydrogen peroxide and peracetic acid into different plastic bags for I.V. solutions during their sterilisation in isolators"
Own investigations, 1999
Publication under preparation.

(4) WALLHAESSER KH:

Praxis der Sterilisation-Desinfektion-Konservierung.
Georg Thieme Verlag Stuttgart, New York.
1988; 265-266.

(5) MATTEWS IP, GIBSON C, SAMUEL, AH:

Enhancement of the kinetics of the aeration of ethylene oxide sterilised polymers using microwave radiation
J.Biomed.mater Res. 1989; 23 (2): 143-146.

(6) HANDLOS VN:

Key technical aspects of gas sterilisation of medical devices.
Risoe Natl. lab.; [Rep.] Risoe-M.1986; Risoe-M-2592: 148 pp

(7) MALCHESKY PS:

Peracetic acid and its application to medical instrument sterilisation.
Artif Organs. 1993; 17 (3): 147-152

(8) BANZER H:

Polymere Werkstoffe, Vol. I.
Theme, Stuttgart, New York. 1985; 372-378

(9) GERLOWSKI LE, KAROS WJ:

Water Transport through Polymers;
ACS Symposium series 423; Barrier Polymers and structures.
American Chemical Society; Washington DC, 1990; 177-191

(10) No author:

PVC im Krankenhaus-Einsatzbereiche, Risiken, Alternativen im medizinische Bereich.
Greenpeace, 1995.