Dosage forms of parenteral route

Injections

Institute of Pharmaceutical Technology and Biopharmacy

History

1616	HARVEY	Discover the bloodstream
1656	WREN	I.v.injection to a dog (opium)
1668	MAJOR	I.v.injection to a human
1850’s	WORD, HUNTER	Subcutaneous injection
1853	PRAVAZ	Develop the first syringe
1860	PASTEUR, LEUWENHOEK	Discover the bacteria
1886	LIMOUSIN, FRIEDLANDER	First ampoule
1782-1896	SCHEELE, VICARIO	Sterilization in practice
1911		i.v. glucose
1920		Oil in emulsion
1950		Oil in emulsion – nutrition

History

1913		haemodialysis
1918	Zsigmondi-Bachmann	Membrane filter
1926		Radiotherapy i.v.
1911		pyrogens
1923		endotoxins
1969		Limulus test
1940		HEPA filters
1961		Laminar flow - HEPA filters
1988		LAL-test validation guides (USA, FDA)

HEPA filter = high-efficiency particulate air filter

Efficacy to the particles that are larger than 0.3 micron = 99,97%

Parenteral preparations

- **Injections**
- Infusions
- Powders or tablets for injections or infusions
- Implants
- Parenteral nutrition
- Haemodialysis solutions

Parenteral preparations Ph.Eur. 6

INJECTION

„Injections are sterile solutions, emulsions or suspensions. They are prepared by dissolving, emulsifying or suspending the active substance(s) and any added excipient in water, in a suitable non-aqueous liquid, that may be non-sterile where justified, or in mixture of these vehicles."

INFUSION

„Infusions are sterile, aqueous solutions or emulsions with water as the continuous phase. They are usually made isotonic with respect to blood. They are principally intended For administration in large volume. Infusions do not contain any added antimicrobial preservatives."

Microbiological purity

Ph. Eur.

Category 1.

„Preparations required to be sterile by the relevant monograph on the dosage form and other preparations labeled sterile.”

Ph.Eur.6 – Microbiological quality of pharmaceutical preparations

categories	Preparations	Requirements
1.	Preparations required to be sterile by the relevant monograph on the dosage form and other preparations labelled sterile.	Sterility
2.	~ for topical use and for use in the respiratory tract, except where required to be sterile, and transdermal patches.	Total viable aerobic count. Not more than 100 micro-organisms (aerobic bacteria plus fungi) per gram, per millilitre or per patch (including the adhesive and backing layer). Transdermal patches: absence of enterobacteria and certain other gram-negative bacteria, determined on 1 patch (including the adhesive and backing layer). Other preparations: mot more than 10 enterobacteria and certain other gram-negative bacteria per gram or per millilitre. Absence of Pseudomonas aeruginosa, determined on 1 g, 1 ml or 1 patch (including the adhesive and backing layer). Absence of Staphylococcus aureus, determined on 1 g, 1 ml or 1 patch (including the adhesive and backing layer).
3.	A./ preparations for oral and rectal administration B./ preparations for oral administration containing raw materials of natural (animal, vegetable or mineral) origin for which antimicrobial pretreatment is not feasible and for which the competent authority accepts microbial contamination of the raw material exceeding 1000 viable micro-organisms per gram or per millilitre. Herbal medicinal products described in category 4 are axcluded.	A./Total viable aerobic count. Not more than 1000 bacteria and not more than 100 fungi per gram or per millilitre. Absence of Escherichia coli (1,0g or 1,0ml) B./ Total viable aerobic count. Not more than 10000 bacteria and not more than 100 fungi per gram or per millilitra. Not more than 100 enterobacteria and certain other gram-negative baceria per gram or per millilitre. Absence: Salmonella (10,0 g or 10,0 ml) Escherichia coli (1,0 g or 1,0 ml) Staphylococcus aureus (1,0 g or 1,0 ml)
4.	Herbal medicinal products consisting solely of one or more herbal drug (whole, reduces or powdered). A ./ Herbal medicinal products to which boiling water is added before use. B./ Herbal medicinal products to which boiling water is not added before use.	A./ Total viable aerobic count. Not more than 10^7 bacteria and not more than 10^5 fungi per gram or per millilitre. Not more than 100 Escherichia coli per gram or per millilitre. B./ Total viable aerobic count. Not more than 10^5 bacteria and not more than 10^4 fungi per gram or per millilitre. Not more than 1000 Escherichia coli per gram or per millilitre. Absence: Salmonella (10,0 g or 10,0 ml) Escherichia coli (1,0 g or 1,0 ml)

Differences between infusions and injections

Aspects	Injections	Infusions
purpose	parenteral drug application	water and ions replacement, parenteral nutrition, praenteral drug therapy
equipment	syringe with needle	infusion bags, cannulas…
applyed amount	Max. 20-50 ml	measured in liters
application time	Max. 15-20 min.	more hours
solvent	water, ethanole, glicerol, propylenglicole, oils, etyl-oleate …	water
Isohydration	not required	required
Isotonicitation	not required	required
Isoionisation	-	recommended
Colloid osmotic pressure	-	recommended by plasma replacements
container	ampoula	infusion bags
Pyrogens	not required	required
Physico-chemical properties	it may be a suspension	solution or o/w emulsion
application area	anywhere	i.v., intraperitonal or subcutaneuous

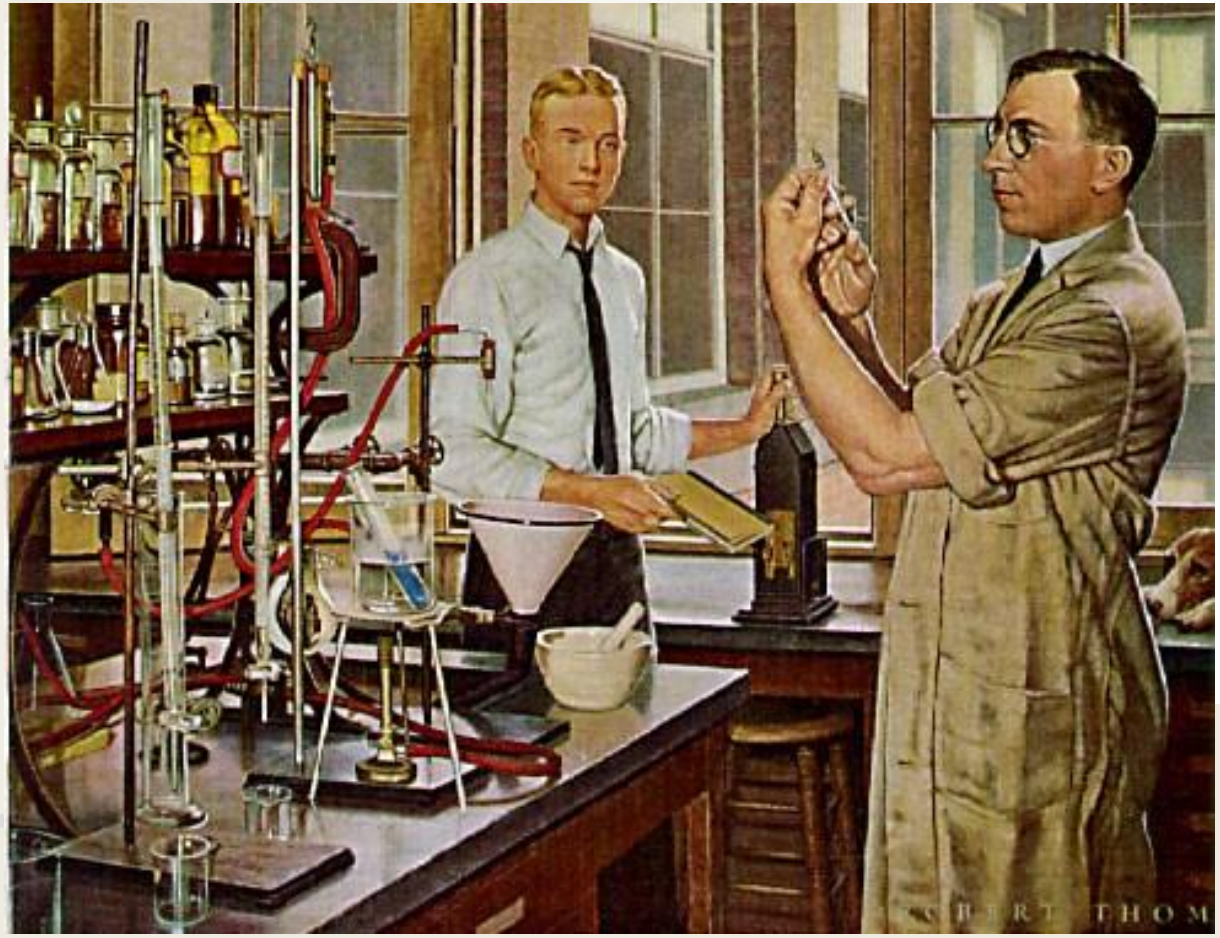
Safety pin

Figure 3. **During Injection:**
Release air in the barrel as usual, Press the plunger forward as an ordinary way to the end of barrel.

Figure 4. **After injection:**
Pull the needle out of human body, then pull the plunger backward until it stops completely, Press the plunger downward to break it.

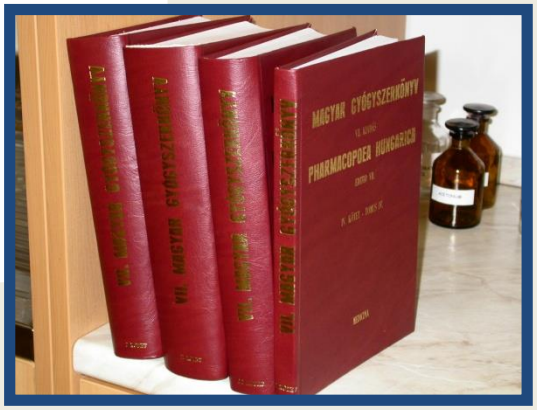
Figure 5. **Break the plunger:**
The needle and retractable mechanism tilt stay inside of the barrel tightly.

Preparation of injections



Institute of Pharmaceutical Technology and Biopharmacy

Injections



- Max. 50 ml
- Sterile
- Solution, emulsion, suspension

- **Evaluation and examination of powder ampoules are the same**
  - These contain dissolvable or dispergable solid materials (powders, lyophilized materials, tablets) filled into sterile ampoule or container, which is made or directly before use made with proper solvent

Injections

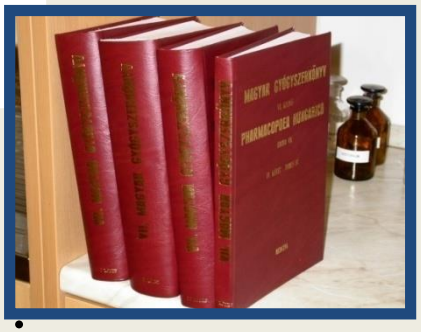
Advantage:

- rapid
- absence of first-pass effect
- controlled blood level of drug
- It may be administered to patients, who can not swallow
- Local or depo effect can be achieved with special injection

Disadvantage:

- Dangerous
- Expensive
- Pain (i.m. !!!)
- It may be administered by qualified person (GP).

Preparation of injections



- Active substance
  - For the preparation of injections and infusions pyrogen-free and microorganism-poor materials have to be used.
  - The microbiological property, purity of APIs and excipients must be adequate to ensure the manufactured production conformity with the standards of microbiological purity regarding to pharmacopoeia.

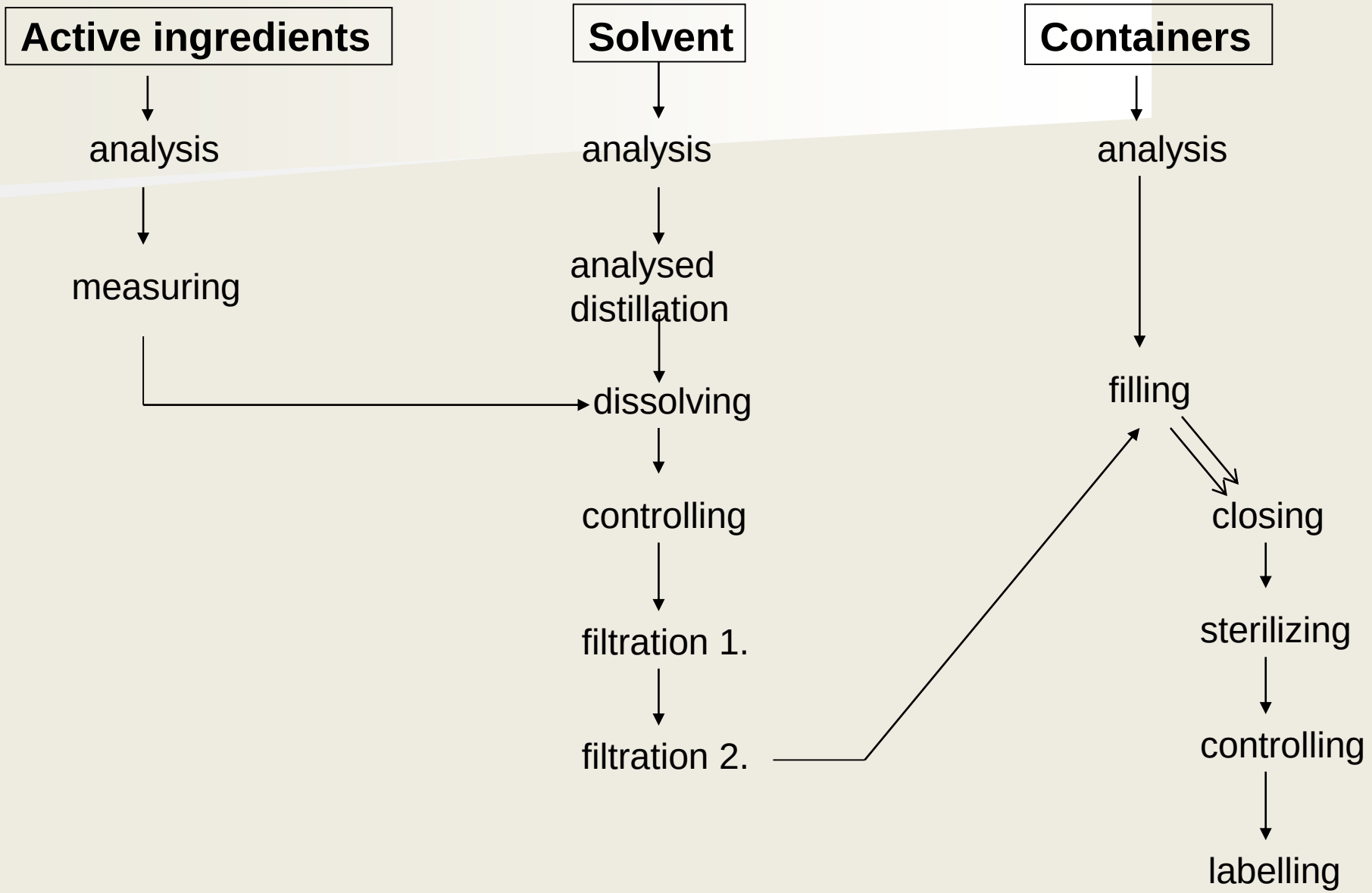
Preparation of injections

- solution
- emulsion
- suspension
- solid (crystalline)
  - lyophilised active substances
  - powder ampoules

Active ingredients

- Must be examined with thorough examination
- From materials with appropriate stability
  - During the preparation and storage do not happen degradation and undesirable change (oxydation, hydrolysis, polymerization)
- Therapeutic value does not decrease

Preparation of injections



Excipient

- „Vehicle is a carrier, composed of one or more excipient, for the active substance(s) in liquid preparation.”

- They are used to ensure the physico-chemical stability of active substance(s).
- The amount of excipient may not be more than required.
- They are not toxic in the required concentration.

Excipient

- hydrotropic substances (assisting the dissolution)
- isotonising ~
- surface active ~ (surfactants)
- viscosity increasing ~
- antioxidants
- buffer-systems
- antimicrobial preservatives

1. Solubility increasing excipient

Macromolecular disperse systems are formulated by ~

active substance + excipient = water soluble adduct

e.g.	acetamide	→	riboflavine
	ascorbic acid	→	riboflavine
	boric acid	→	calcium-gluconicum
	diethyl acetamide	→	barbital
	urea	→	quinine
	sodium-salicylate	→	caffeine, theobromide
	nicotinamide	→	caffeine, theophylline

Colloidal disperse systems are formulated by ~

solubilisation

2. Chemical stabilizer

- Decrease of storage temperature
- Adjusting the oxidation potency (pH effect)
- Applying redox systems (antioxidants)
  - inorganic sulfur derivatives (sodium-bisulphite, sodium-pirosulphite)
  - Organic sulfur derivatives (cystein)
  - Ascorbic acid
- Exclusion of oxygen (N_2, CO_2 - gas)

3. Microbiological preservatives

Preservatives	Applied concentration (%)
Methyl-p-hydroxy-benzoate	0.08-0.1
Methyl-p-hydroxy-benzoate + propyl-p-hydroxy-benzoate	0.05-0.088 + 0.011-0.03
Trichloro-isobutyl-alcohole	0.1-0.6
phenol	0.06-2.5
Tricresol	0.1-0.4
Chlorcresol	0.1-0.2
Phenyl-mercury(II)-acetate, -borate, merthyolate)	0.0005-0.002-0.1
Metacresol	0.1-0.3
Benzalkonium-chloride	0.005-0.02
Cresol	0.1-0.15

4. Excipient, that comply the physiological requirements

- **Isotonicity**
  - NaCl
  - The anisotonic solution may cause pain, and tissue damage.
- **Isohydration**
  - HCl, NaOH, $NaHCO_3$, buffer-solutions
- **Colloid osmotic pressure**

Routes of administration

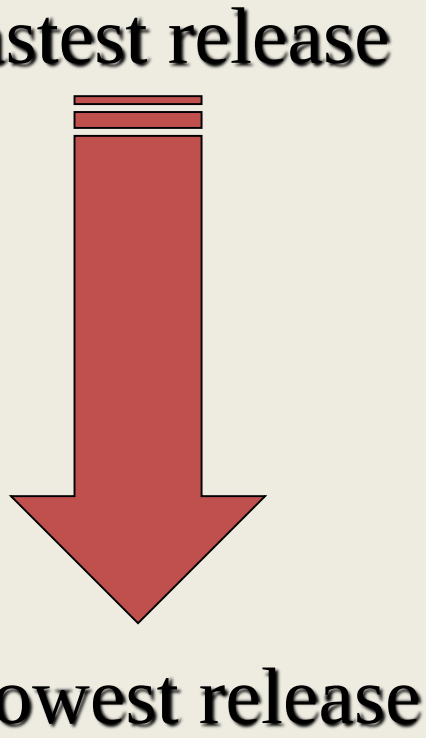
Administration	Abbrev.	Comment
Intraarterial	ia.	Rarely applied
Intraarticular	-	Into joint cavern
Intragluteal	-	Into the buttock (m. gluteus). Oil based solutions. Depot effect
Intracardial	-	Into the heart muscle
Intracutaneous (intradermal endermal)	ic.	Local anesthetics
Intralumbal (intraspinal, intrathecal, subdural, subarachnoidal)	-	lumbalanesthesia
Intramuscular	im.	Into the muscle. Water based solutions. Rapid absorption. Max 100ml

Routes of administration

Administration	Abbrev.	Comment
Intranasal	-	Beneath the surface of nasal mucosa
Intraneural	-	Into nerve
Intraperitoneal	ip.	(abdominal cavity)
Intrapleural	-	(chest cavity)
Intravenous	**iv.**	**Most common route**
Perineural	-	Into the nerve tissue
Retrobulbar	-	Behind the eyes , max. 5ml
Subconjuctival	-	Beneath the conjuctiva; 0,5-1 ml
Subcutaneous	sc.	Beneath the skin surface. (subcutaneous drop-infusion)

The effect length of different injections

- water based solution
- water based suspension
- oil based solution
- o/w emulsion
- w/o emulsion
- oil based suspension



Requirements of solvents

a) **Physical conformity**
b) **Toxicological conformity**
c) **Chemical compatibility**
d) **Physiological conformity**

Solvents

1, Aqua ad iniectabilia

2, Non-aqeous solvents

- hydrophilic
  - Ethanol
  - Glycerol
  - polyethylene-glycol (PEG)
  - butylene-glycol
  - benzyl-alcohol

- lipophilic
  - fatty oils (plant origin)
  - ethyl-oleate
  - benzyl-benzoate
  - isopropyl-myristate
  - oleum neutrale

Requirements of solvents

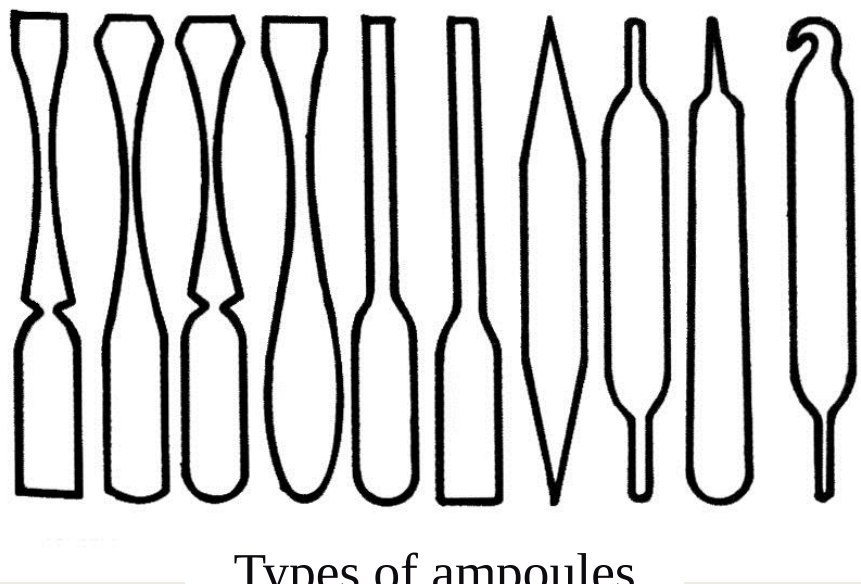
1) Indifferent (body, preparation)
2) Miscible (e.g. with blood)
3) Non toxic
4) Non irritable
5) Affordable
6) Appropriate solvent
7) Appropriate stability
8) Retain liquid state in a wide temperature range
9) pH-inert
10) Sterile or may be sterilized
11) Appropriate physical properties

Technology of preparation process

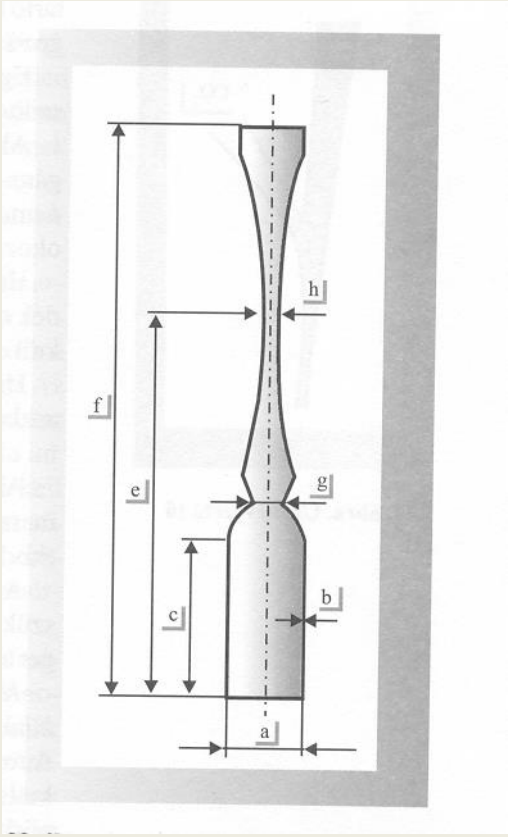
1. Cleaning of ampoules
2. Sterilization of ampoules
3. Preparation of the injectable solution
4. Filtration
5. Filling into ampoules
6. Soldering of the ampoules
7. Sterilization of injections
8. Closing tests of ampoules
9. Examinations of preparations
10. Labelling

Containers

-glass (injections)
-plastic (infusions)



Types of ampoules



ampoule

5. Filling into the ampoules

- syringe and needle
- burettes and „filling-pen”
- Hahn-pipette
- Automatic equipment

Into the injections containers, the injected or filled volume have exceed the declared volume, to be able to use the effective namely the nominal volume.

For example: with label 5 ml, 5.3 ml have to be filled

The necessary data referred to this are in right table of the pharmacopoeia

K/4. táblázat

A jelzett mennyiség ml-ben	Az injekció tényleges térfogata ml-ben	
	Kis viszkozitású oldatok (50 mPa·s-ig)	Olajos oldatok, emulziók, szuszpenziók vagy viszkózus oldatok (50 mPa·s fölött)
0,5	0,6	0,65
1,0	1,1	1,2
2,0	2,2	2,3
5,0	5,3	5,5
10,0	10,5	10,7
20,0	20,6	20,9
20 ml fölött	+3%	+4%

Technology of preparation process

1. Cleaning of ampoules
2. Sterilization of ampoules
3. Preparation of the injections
4. Filtration
5. Filling into ampoules
6. Sealing of the ampoules
7. Sterilization of injections
8. Closing tests of ampoules
9. Examinations of products
10. Labelling

Examinations of injections

Examination (Ph. Hg. VII.)

1. Characters
2. Dosage form
3. Assays
4. Packaging
5. Storage

Examination of dosage form

1. Colour. Mechanical impurities
2. Volume
3. Homogeneity and homogenisation
4. Consistency of oil based injections
5. Particle size of suspension injections
6. pH
7. Uniformity of dosage units of vials
8. Solubility of vial's content
9. Uniformity of dosage units of tablets for injectable solutions
10. Solubility of tablets for injectable solutions

1. Colour. Mechanical impurities

The injectable solutions have to be ***always clear***, and does not have to contain: ***filaments, shreds, shard of glass***.

They have to be colorless, or their color do not be more intensive than the particular color sample solution.

The color intense of each manufactured unit filled into ampoule have to be equal under the particular color sample solution.

1. Colour

a) The completed ampoule comparison with the *colour sample solutions*

b) 5.0 ml from the ampoule is compared with 5.0 ml of colour sample solution

1. Mechanical impurities

a) In front of black background, in a dark place, use of 60 W lamp

b) Two, independent investigator people

c) Many times rotated, with a side and crossed light within 15 seconds from 30 cm distance

Filament examination

1. Qualitative, non-destructive

2. Quantitative, destructive

Qualitative non-destructive tests

- Visual control:
  - without magnifying glass,
  - with magnifying glass
  - in a polarized light (with enlargement)
  - Tyndall effect (light reflection) use enlargement or not
  - after centrifugation, in the storage
- Automated machine-photocell (electronics)
- Nephelometry
- Automatic reflection measuring machine

Quantitative, destructive tests

Take care:

- to represent the total batch with the samples, examined
- to avoid the contamination during measuring the trial and during the examination

Quantitative, destructive tests

- Membrane filtering and microscopic particle counting
- Conductometric particle counting (Coulter-Counter®)
- Particle counting based on reflection (Zetasizer)

Examination of dosage form

1. Colour. Mechanical impurities
2. Volume
3. Homogeneity and homogenisation
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Volume of injections

Labelled volume (ml)	Number of examined ampoule
0.5	10
1.0	10
2.0	10
3.0	5
5.0	5
10.0	5
20.0	5
50.0	3

The volume of injections must not be less than the labelled amount.

Uniformity of single dose (volume)

- 20±2 °C
- In the tool which in the measurable volume fill the 40 % of scaled volume
- Suspension has to homogenous during the test
- In the case of 10 ml or less volume the test has to be done with syringe with scale divided by 0.1 ml
- The examination of injections with more than 10ml has to be done with controlled measuring cylinder

Examination of dosage form

1. Colour. Mechanical impurities
2. Volume
3. Homogeneity and homogenisation
4. Consistency of oil based injections
5. Particle size of suspension injections
6. pH
7. Uniformity of dosage units of vials
8. Solubility of vial's content
9. Uniformity of dosage units of tablets for injectable solutions
10. Solubility of tablets for injectable solutions

4. Consistency of oil based injections

Ph.Hg.VII.:

Vertically down held 1.00 ml of oil based preparation from injection syringe:

- In case of oily solution within at most 45 s,
- In case of oil based suspension within at most 180 s to flow out.

Examination of dosage form

1. Colour. Mechanical impurities
2. Volume
3. Homogeneity and homogenisation
4. Consistency of oil based injections
5. Particle size of suspension injections
6. pH
7. Uniformity of dosage units of vials
8. Solubility of vial's content
9. Uniformity of dosage units of tablets for injectable solutions
10. Solubility of tablets for injectable solutions

Particle size of the suspended injections

Ph.Hg.VII.:

- Suspended particle size
  - 80%➔ 5-30 μm,
  - 20%➔ max. 80 μm

Examination of dosage form

1. Colour. Mechanical impurities
2. Volume
3. Homogeneity and homogenisation
4. Consistency of oil based injections
5. Particle size of suspension injections
6. pH (range: pH 3-8)
7. Uniformity of dosage units of vials
8. Solubility of vial's content
9. Uniformity of dosage units of tablets for injectable solutions
10. Solubility of tablets for injectable solutions

Examination of dosage form

1. Colour. Mechanical impurities
2. Volume
3. Homogeneity and homogenisation
4. Consistency of oil based injections
5. Particle size of suspension injections
6. pH
7. Uniformity of dosage units of vials
8. Solubility of vial's content
9. Uniformity of dosage units of tablets for injectable solutions
10. Solubility of tablets for injectable solutions

Uniformity of dosage units of vials

Labelled mass (mg)	Limits (%)
20-150	±10
151-300	±7.5
>300	±5

Examination of dosage form

1. Colour. Mechanical impurities
2. Volume
3. Homogeneity and homogenisation
4. Consistency of oil based injections
5. Particle size of suspension injections
6. pH
7. Uniformity of dosage units of vials
8. **Solubility of content of vials**
9. Uniformity of dosage units of tablets for injectable solutions
10. Solubility of tablets for injectable solutions

8. Solubility, and dispersible property of content of vials

- to be homogeneous
- lyophilized material should not shrunk
- the components dissolve clearly in the prescribed solvent without remains, or in the case of suspension preparation must be dispersed equable

Examination of dosage form

1. Colour. Mechanical impurities
2. Volume
3. Homogeneity and homogenisation
4. Consistency of oil based injections
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7. Uniformity of dosage units of vials
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Component examination

- Identification examination (Identification)
- Purity examination (Impurities)
  - *Water content of vials*
    not more than 1.0%
  - *Microbiological purity*
    injection must be sterile
  - *Pyrogens* - ***more than 5 ml***
    - Active ingredients can give the pyrogenereaction
- Content examination (Assay)
  - API content determination

Suspension injections

In case of:

- incorporation of low solubility or insoluble substances
- ensuring the depo effect

- **Vehicle can be:**
  - water,
  - oil-based
- **APIs can stored in:**
  - suspension
  - vial

Excipients involve:

- viscosity increasing
- wetting ensuring
- assistance of shakable property
- stabilizating
- isotonisating
- puffer
- preservative

Suspension injections

viscosity

- ***hydrogel suspensions***
  - methyl-cellulose
  - Sodium carboxyl-methyl-cellulose
  - PVP
  - dextran
  - Mucilage of sodium-alginate
- ***Oil based suspensions***
  - aluminum stearate

Oil based suspension injections

- ***Preservatives***
  - phenol
- Particle size: < 5 μm
- The slow onset of drug action:
  - B12-vitamine contained aluminium-stearate gel
  - procaine-penicilline G

Microparticulate suspension

Properties:

- filled into vials
- proper vehicle
- depot effect

substances:

- chloramphenicole (Chlorocid)
- hydrocortizone
- penicillin preparations, depot action (Retardillin)

Suspension can be prepared from solution by separation:

- Change of solvent
- Mucus associates the precipitation
- Precipitation helping excipient (crystals)

Vials, lyophilized powders, tablets I.

- Vials (powder ampoules):
  - In case of an API or a component can not be stored in dissolved form without adverse change
    - prepare in aseptic way
    - with automated dosing machine
    - sterilization according to nature of used material

Vials, lyophilized powders, tablets II.

- Vials
  - filling: into wide-necked ampoules/ vials
  - close: with rubber or plastic plug

  which has to be penetrable to inject the solvent or to take out solution from the vials, without removing the stopper
  - risk of cross-crystallization, crystal-growth minor
  - composition has to dissolve with in 3 minutes, **clearly**

Vials, lyophilized powders, tablets III.

- Lyophilized materials
  - manufacture: with lyophilization method, cryodehydration

- lyophilized material should not shrunk; shaking has to be dissolve in appropriate solvent clearly without residuals ***within 3 minutes***

Vials, lyophilized powders, tablets IV.

- Tablets
  - prepare under aseptic circumstances
  - can be sterilized with ethylene oxide gas
  - e.g. preparation of procaine chloride, adrenaline
  - examination:
    - *unique and average mass*
    - *solubility*

Vehicles

- Water-based suspension
- Oil-based suspension
  - Olive oil, sasame oil, peanut oil

THANK YOU FOR ATTENTION!