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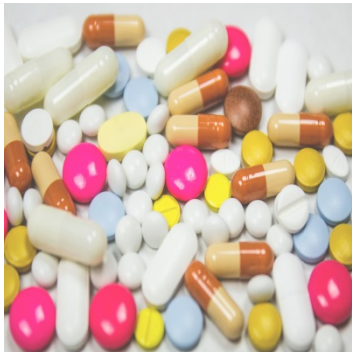


Ready to administer – everything under control?

Gothenburg March 2018 Stefanie Sauer

UK HD

Disclosure

Relevant Financial Relationship

None

Off-Label Investigational Uses

None

Self-assessment questions

1) Ready-to-administer preparation(RTA): medicinal product at the required concentration and volume in the final container such as syringe.

2) For most iv-preparations it‘s recommended that they meet with the requirements of GMP.

3) It‘s not necessary to measure pressure in cleanrooms.

Learning objectives

- Definition Ready-to-use / ready-to-administer
- Considerations before starting the production
- Examples of different formulations of RTU / RTA formulations in Heidelberg and their preparation
- Quality control (environmental, microbiological, chemical-physical)
- Available products on the market

Definition

- Ready-to-administer preparation(RTA): medicinal product at the required concentration and volume in the final container such as syringe
- Ready-to-use preparation (RTU): medicinal product at the required concentration and volume in a container. The content has to be transferred into the final administration device prior application e.g. in a syringe or infusion bag

Advantages and disadvantages RTA / RTU

- Fixed concentration
- Convenient
- Fast application (emergency)
- Medication safety ↑
- Patient safety ↑
- Costs

- Fixed concentration
- Stability
- Costs

Considerations before starting the production

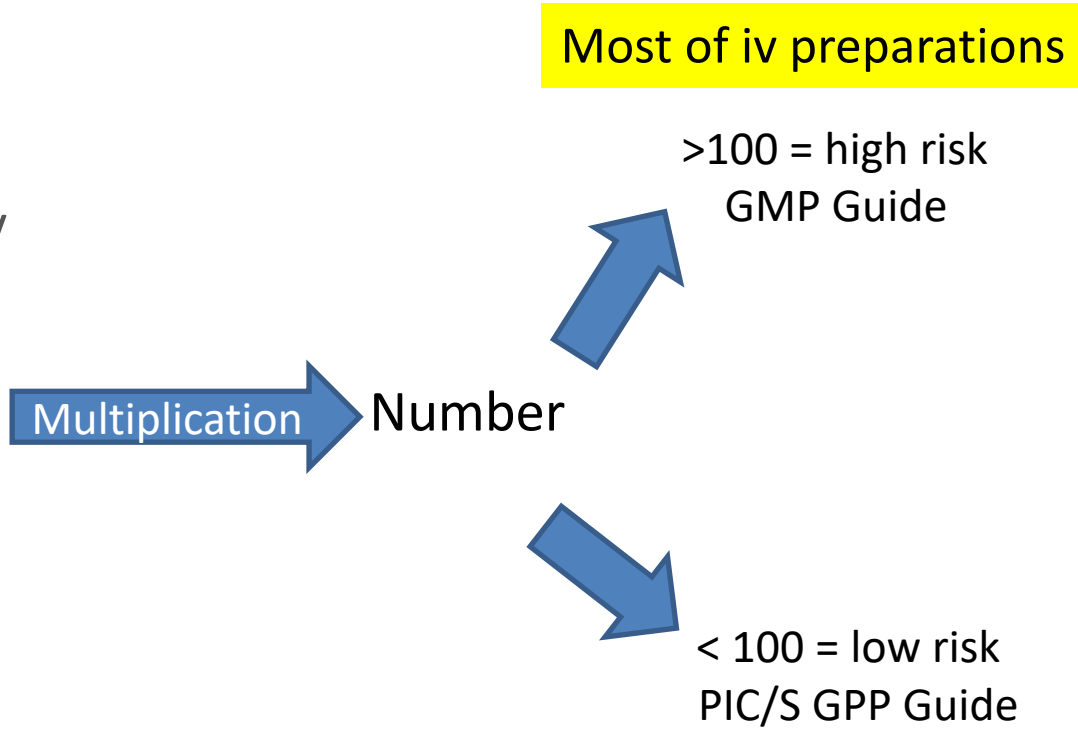
- Any product on the market (EDQM resolution 2016)?
- Chemical-physical stability? Literature? Own stability testing?
- Microbiological stability? Existing facilities? Risk assessment, validation
- Extratemporaneous formulation vs. batch production
- Costs
- EDQM: High risk preparation vs. Low risk preparation

Risk assessment high or low risk

- Possible model procedure for risk assessment
- Which quality control system is recommended?
- Risk assessment should consider different items of the preparation and the active substance → 5 Sections are listed
- In these sections decision criteria are specified, each decision criterion has a risk factor from 1 to 5, multiplication of theses factors results in a number

Risk assessment high or low risk

1. Type of preparation
2. Amount prepared annually (units)
3. Pharmacological effect of the active substance
4. Preparation process
5. Supply



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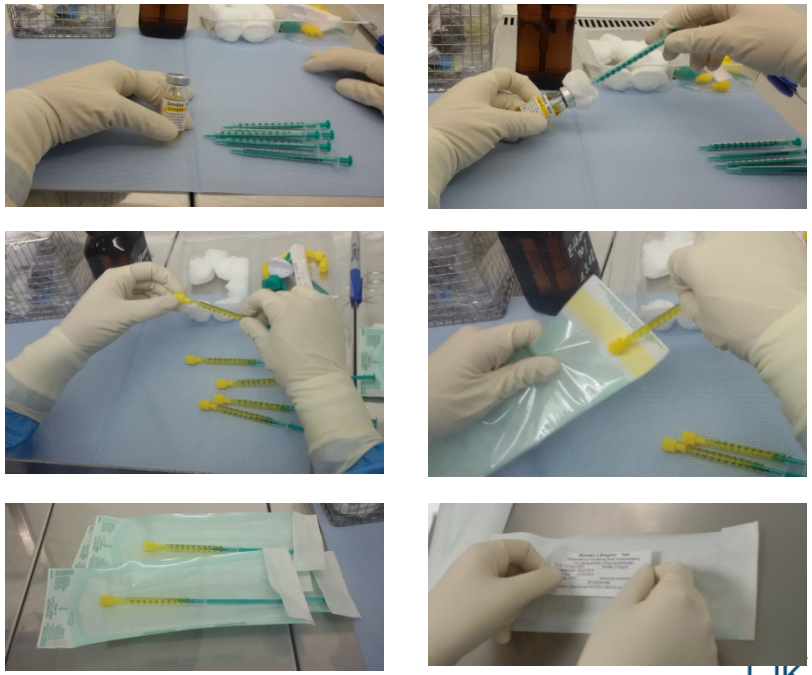
PREPARATION

Example 1: Subdivision of Levosimendan

- Preparation for children to avoid discarding
- Expensive product
- Extratemporaneous formulation → RTA
- Indicated by chronic heart failure

Example 1: Subdivision of Levosimendan

- Preparation under laminar air flow (clean room A) in a surrounding clean room C
- One ampoule = 5ml → division into 5 parts of 1ml in a syringe



Example 2: Dilution of Indometacin (meglumine)

- Is used for the closure of the ductus arteriosus in prematurely born children
- Used concentration 0,1mg/ml → not available on the market
- No discarding

Example 2: Dilution of Indometacin (meglumine)

Preparation of a solution (laminar air flow):

Indometacin (dry powder) dissolving with the attached solvent

→ Indometacin (dissolved) 50 mg/ 2 ml

498 ml NaCl 0,9% + 2 ml Indometacin (dissolved) 50 mg/2 ml

→ 500ml Indometacin (dissolved) 0,1 mg/ml

Division into parts of 10ml

Example 3: Solutions with Epinephrine and Norepinephrine

- History: In 2008 intensive care unit wants the preparation of syringes for the emergency case, immediate available
  - Raise concerns over hygienic and dosage quality
  - Best production in the pharmacy unit
- Different products:
  - Epinephrin 100µg/ ml
  - Epinephrin 10µg / ml
  - Norepinephrin 100µg / ml
  - Norepinephrin 10µg / ml

Example 3: Solutions with Epinephrine and Norepinephrin

But: How to meet the great demand on syringes?

Batch production with a syringe filler

About 300 syringes / hour

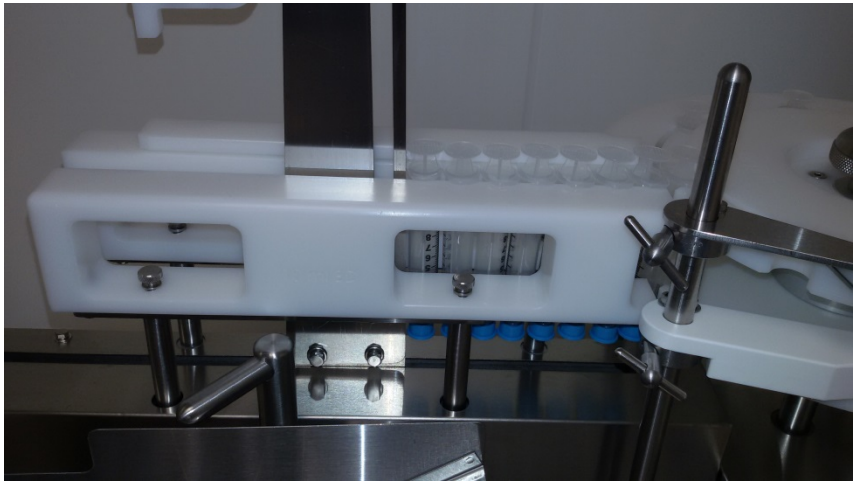
Example 3: Solutions with Epinephrine and Norepinephrin

- Preparation:
  - bulk solution under laminar air flow (3000ml)
  - In-process control
  - Division of the bulk with the help of the syringe filler
  - Labelling the syringes per hand
  - Packaging of the syringes
  - Control

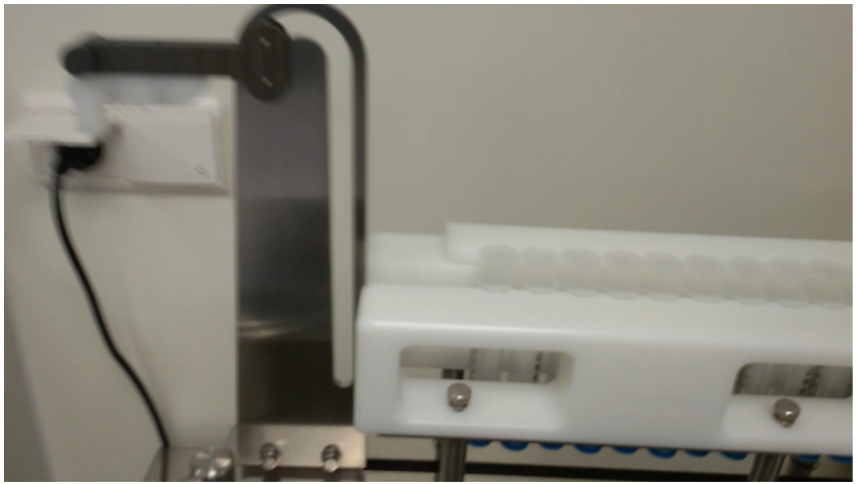
Syringe Filler (Added Pharma)

Syringe Filler (Added Pharma)

Feeding of syringes



Filling station



Different automatic syringe fillers

	Added	Baxa	Plümat
Name	SmartFiller ®	RapidFill ® ASF	Plümatex SF 022
Capacity	400 per hour	600 per hour	225 per hour
Labelling	no	yes	no
Containers	10 – 60 ml	10 ml	10 – 60 ml
Syringes and stoppers from different manufacturers	no	No Strip of syringes	yes
surrounding	Laminar air flow, isolator	Laminar air flow	Laminar air flow, isolator

Example 4: Batch production with terminal sterilization

Batch production with steam sterilization for heat-resistant drugs

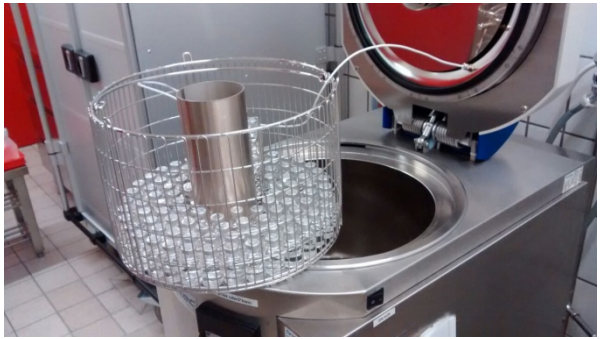
Resulting a RTU formulation

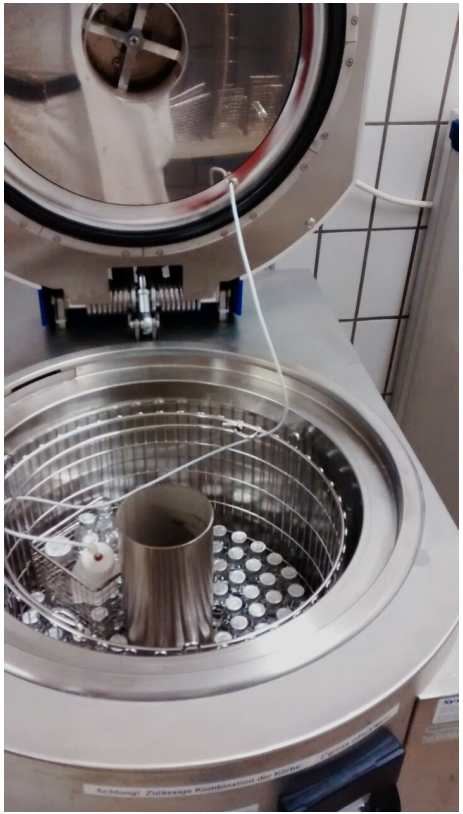
- Application via continuously operating syringe pumps
- Products in Heidelberg e.g.
  - Argartroban 0,5 mg/ml; 50ml
  - Furosemid 1mg/ml; 50ml
  - (Diltiazem-HCl 5mg/ml; 5ml)
  - Clonidin 10µg/ml; 50ml

Example 4: Clonidin 10µg/ml

- Preparing a solution
- In-process control
- Filtration into vials (50ml) under laminar air flow and stoppering the vials
- Steam sterilization (121°C, 2 bar, 15 minutes)
- Labelling
- End control

Batch production with terminal sterilization





Ready to administer – everything under control?

QUALITY CONTROL

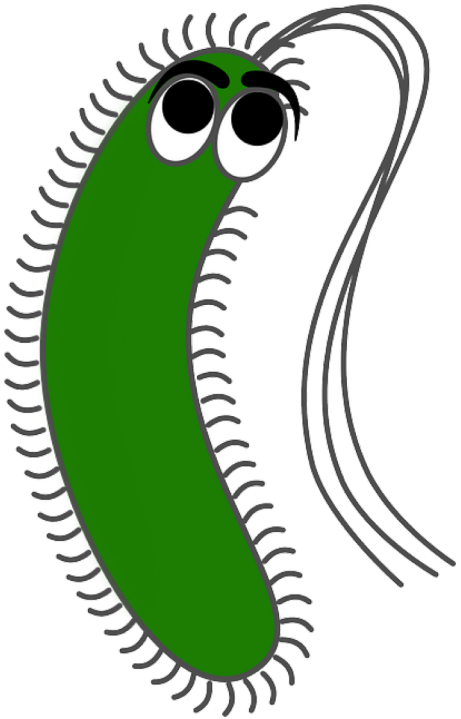
Cleanrooms

- Classified rooms with different locks
- Cleanroom clothing
- Laminar airflow benches
- Qualification of the equipment

Monitoring of the rooms

- Temperature (continuously)
- Pressure (continuously)
- Humidity (continuously)
- Particles (2 times a year)

Microbiological control



- Qualification of the syringe filler via media fill
- Validation of the personnel via media fill
- Settle and contact plates during the filling
- Filtration of the solution (0,22µm) before steam sterilization
- Settle plates in the cleanrooms

Control of the product (Ph. Eur.)

- In-process control before filling
- Protocol
- Filling volumen
- Identity
- Content via UV/Vis or HPLC
- Non-visible particles
- Sterility
- Labelling

Examples for RTU / RTA on the market

- Aguettant (France): Ephedrin, Phenylephrin, Adrenalin, Atropinsulfat, Noradrenalin, Blue Marker
- BD Saline®: NaCl 0,9%
- Argartra ®: Argartroban 1mg/ml
- B. Braun: prefilled flush-syringes, DUPLEX® Container (two-chamber-bag)
- Fresenius Kabi: Simplist® prefilled syringes, FreeFlex® Bags
- And and and…

Bulk solutions SmartPaks (Added Pharma)

Solution bags of 500ml or 1000ml or 5000ml

- Antibiotics: Cefazoline, Ceftriaxone, Cefuroxime
- Analgesics: Morphinsulfate
- Anesthetics: Bupivacaine, Levobupivacaine
- Combinations: Bupivacain and Sufentanile
- Others: Calciumgluconate, Heparin, Sodium Glycerophosphate

Conclusion

Increasing numbers of RTA / RTU in future

Risk assessment and a good planning ist important

Different formulations need different work environment and settings

Quality must be included in production and not only tested

→ Pharmacy unit is an ideal place for producing RTA / RTU if there are no authorised products on the market

3 Take home messages

- RTA / RTU formulations raise patient safety and are a first-class service products
- There are several ways to produce RTA /RTU
- Quality must be included in production and not only tested

→ **Always keep an eye on the entire process**

Self-assessment questions and answers

1) Ready-to-administer preparation(RTA): medicinal product at the required concentration and volume in the final container such as syringe.

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3) It‘s not necessary to measure pressure in cleanrooms.

References and further reading

EDQM resolution 2016
https://www.edqm.eu/sites/default/files/resolution_cm_res_2016_1_quality_and_safety_assurance_requirements_for_medicinal_products_prepared_in_pharmacies.pdf

GMP Guide https://ec.europa.eu/health/documents/eudralex/vol-4_en

Revision Annex 1 GMP Guide https://ec.europa.eu/health/human-use/good_manufacturing_distribution_practices/gmp_developements_en

PIC/S GPP Guide https://www.picscheme.org/layout/document.php?id=156

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