The safety and pharmacoeconomics of ready-to-administer injections

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Aesculap academia

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Facts

- Medication errors kill 7'000 persons each year in the USA *To err is human, 1999*
- Parenteral medication errors are nearly 3 times as likely to cause harm or death compared with other drugs (3% vs 1.2%)

  Am J Health-Syst Pharm 2008;65:2367-79
- The high-risk is related to the **complexity** of the process and the **major clinical impact** for the patient

Risk = probability x consequences

Intravenous medication: errors at each stage

Table 2 Percentages of errors at each stage

Error description	Stage	Median (95% credible interval)
Error in obtaining drug	Stage 1	5.34 (2.59 to 10.3)
Error in obtaining diluent	Stage 2	6.78 (3.02 to 14.1)
Error in reconstituting drug and diluent	Stage 3	31.0 (11.8 to 49.6)
Error in checking patient's identity	Stage 4	0.07 (0.01 to 1.00)
Error in checking for patient allergies	Stage 5	15.1 (0.09 to 57.5)
Error in checking route of drug administration	Stage 6	0.50 (0.12 to 1.19)
Error in checking drug dose	Stage 7	4.11 (1.81 to 8.50)
Error in checking patency of cannula	Stage 8	4.51 (0.62 to 40.3)
Error in expelling air from syringe	Stage 9	1.00 (0.13 to 7.58)
Error in administering drug	Stage 10	21.7 (6.51 to 48.8)
Error in flushing cannula	Stage 11	5.50 (0.54 to 20.5)
Error in signing prescription chart	Stage 12	5.34 (0.55 to 20.2)
Omission error		3.45 (0.84 to 10.1)

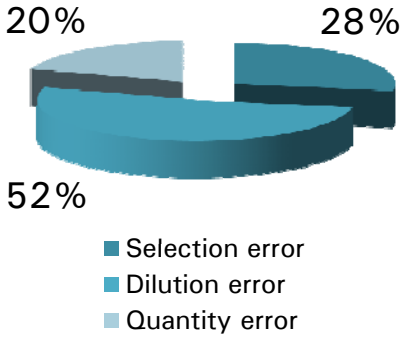
Review – 9 studies

Mc Dowell SE, Qual Saf Health Care 2010;19:341-5

Preparation errors

Simulation study

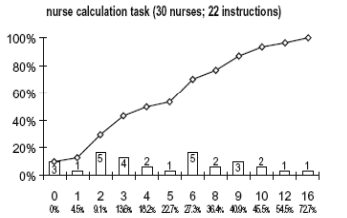
- **Mean rate: 6.5%** (n = 28)

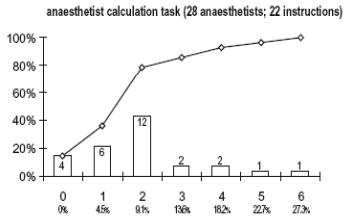


Garnerin Ph, Eur J Clin Pharmacol 2007;63:769

Calculation errors

- **Anaesthesiologists**
  10.4% (n = 28)
- **Nurses**
  26.7% (n = 30)
- **Large interindividual variability**





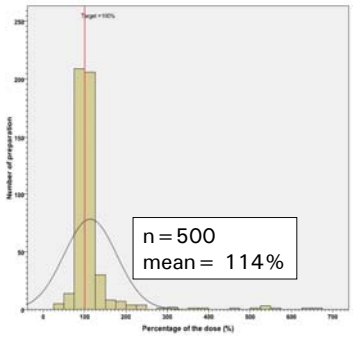
Garnerin Ph, Eur J Clin Pharmacol 2007;63:769

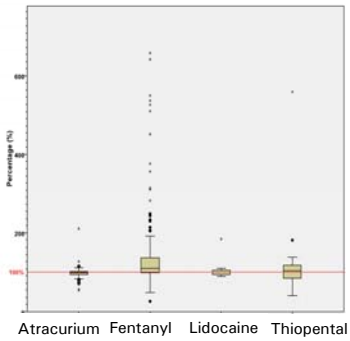
Preparation errors

Real-life study

- **Unused syringes in anaesthesiology**

  > ± 10%: 29% > ± 50%: 8% > ± 100%: 4%





Stucki C, HUG, 2009

Microbial contamination

Simulation study

- **Anesthesiology**
  - Contamination found in
    - 5 / 38 prepared bags (**13%**)
    - in 5 / 20 test patients
    - by 4 / 10 anesthetists

- 10 / 197 syringes (5%)
- 6 / 17 needles (35%)

HUG Real life

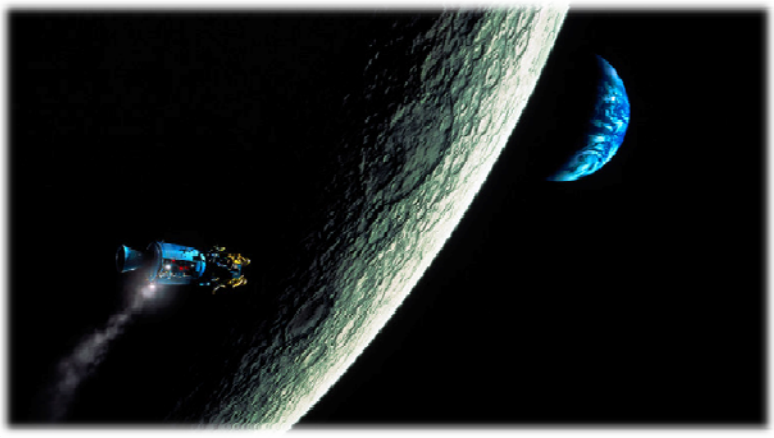
0.5%

2 syringes/day

Stucki C, HUG, 2005

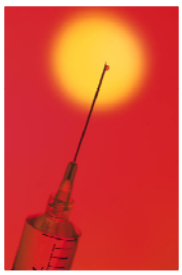
Gargiulo D, BML Quality & Safety 2012, doi:10.1136/bmjqs-2012-000814

Houston, we've got a problem



Global approach to safety

Standardizing drug dilutions and labeling



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Ready-to-use preparations

↓

From the industry → Registration
Outsourcing

↓

From the hospital pharmacy → GMP facility

Standardizing drug dilutions and labelling

- **Intra-institution**
  (emergency, intensive care, anaesthesiology, acute care)
- **Inter-institution**

Gattlen L, CHUV, 2012

Ready-to-use preparations

From the industry

- **Registered**
  - bupivacaine bag for peridural anaesthesiology
  - morphine bag for PCA
  - KCl vial for ICU
- **Outsourcing**
  - heparin vial (Bichsel)
  - ephedrine syringe (Sintetica)

Ready-to-use preparations

From the hospital pharmacy

- Collection of **customer needs**
  - interested clinical areas
  - list of potential drugs
- **Risk assessment** ➡ priority list
  (probability of occurrence x consequences)
- **Feasibility** study
- **Stability** assessment
- Starting **batch production**
- Research of **industrial partnership**

Ready-to-use preparations

From the hospital pharmacy

	Stability	Qty/yr
Phenylephrine 1mg = 10mL	1 year (room T°)	12'000
Insuline 50UI = 50mL	6 months (4°C)	7'000
Suxamethonium 100mg = 10mL	6 months (room T°)	6'000
Atropine 1mg = 10mL	1 year (room T°)	2'000
Cefuroxime 5mg = 0.5 mL	4 months (-18°C)	2'000
Caffeine citrate 10mg = 1mL	1 year (room T°)	1'800
Ketamine 10mg = 10mL	7 months (room T°)	1'000
Vancomycine neonat 50mg = 10ml	6 months(4°C)	1000
Isoprenaline 5mg = 50mL	6 months(4°C)	200
3 ophtalmic injectables – Ceftazidine 22.5mg = 1mL – Dexamethasone 4mg = 1mL – Vancomycine 10mg = 1mL	6 months (-18°C)	150

Total: 30'000 (batch) + 2'000 (individual)

Is it safer ?

Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gordon C S Smith, Jill P Pell

Results We were unable to identify any randomised controlled trials of parachute intervention.

Parachutes reduce the risk of injury after gravitational challenge, but their effectiveness has not been proved with randomised controlled trials

Smith G, BMJ 2003;327:1459-61

Ready-to-use preparations

From the hospital pharmacy

- **Why it is safer:**

  Changing the paradigm…

  Good
  Manufacturing
  Practices

GMP

- **Rooms** (cleanrooms, isolators / laminar airflow hoods)
- **Operator's training** (qualification)
- **Working process** (validation, informatic tools)
- **Documentation** (standardized production protocols)
- **Quality control** (products, cleanrooms, operators, …)
- **Traceability** (whole process)

Improved safety ?

- **Suppress opportunities for errors**
  - Production protocols and procedures (chemical)
  - Computer-assisted production management (chemical)
  - Clean environment (microbiological)
  - Specifically trained operators (chemical, microbiological)
- **Intercept errors before they reach patients**
  - Quality control (chemical, microbiological)

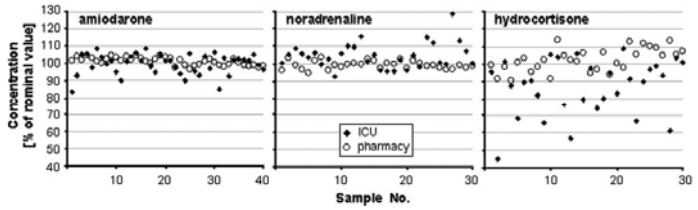
Computer-assisted production management

- Operator ID
- Balance selection
- Raw material ID
- Weighing check and registration

Improved safety !

- **Deviation >10%:**
  - 22% of the ICU manually prepared samples
  - 5% of samples from pharmacy machine-made solutions
- **Mean concentrations:**

ICU: 97.2% (45–129%) Pharmacy: 101.1% (90–114%)



Dehmel C, Intensive Care Med 2011;37:1311-6

Errors detected by the quality control !

Microbiological safety

- Isolator in class C (ISO7) GMP cleanroom
- Sterilisation with H_2O_2
- Filling with a Smartfiller pump

Microbiological safety

- **Simulation studies (media-fill testing)**

Table 1.
Rates of Syringe Contamination by Environments and Types of Manipulation (n = 1500)

Environment[a]	% Contamination by Type of Manipulation					
	Simple Filling	Air Introduced Into Syringe	Syringe Without Cap	Syringe Tip in Contact With Fingers	Syringe Tip in Contact With Object	Total % Contaminated Syringes
Cleanroom[b]	0	0	0	0	0	0
Operating room	0	0	1	24	3	6
Ward	0	0	1	10	67	16
Total %	0	0	1	11	23	7

[a] n = 100 for each condition and type of manipulation; the total number of syringes tested was 1500.
[b] Horizontal laminar-airflow hood in International Organization for Standardization class 5 cleanroom.

Stucki C, Am J Health-Syst Pharm 2009;66:2032-6

Pharmacoeconomics

Costs of ready-to-use syringes

- **Investment costs**
  - Cleanroom class C (20 m² x 8'000 €/m²) 160'000 €
  - Isolator 125'000 €
  - Filling machine
    - Baxa Repeater 5'000 €
    - Smartfiller (human ressources ÷ 2) 125'000 €
  - **Total** (depending filling system) **290'000 - 410'000 €**
  - **5 year amortization** **58'000 - 82'000** €/year
  - **Idem without cleanroom** **26'000 - 51'000** €/year
  - In our case: 250'000 € / 5 year = 1.6 € / syringe

Pharmacoeconomics

Costs of ready-to-use syringes

- **Development costs (stability study)**
  - Development and validation of a stability-indicating quantitative analytical method
  - Stability study

– **Total cost**	**10'000 €**
– **Cost / syringe** (5'000 syringes/year, over 5 years)	**0.40 €**

Pharmacoeconomics

Costs of ready-to-use syringes

- **Production costs (€)** **(Phenylephrine 1mg = 10mL)**

Batch size	1000	2000	Nurse
– Product materials	2.00	2.00	1.10
– Isolator materials	0.80	0.40	
– Human ressources	1.00	0.80	*4.00
– Quality control	0.20	0.10	
– Total	4.00	3.30	5.10

* 5 minutes/syringe

(Hecq JD, Ann Pharm Françaises 2011;69:30-7)

Pharmacoeconomics

Benefits of ready-to-use syringes

- **Cost-avoiding**
  - Syringes produced — 30'000/year
  - Rate of errors — 5% — 1'500/year
  - Ratio errors : serious ADE — 1% — 15/year
    Bates D, J Gen Intern Med 1995;10:199
  - Cost by serious ADE — 4685 $ — **53'400 €/year**
    Leape L, JAMA 1999;281:267 (=3560 €) **1.80 € /syringe**
- **Cost-saving**
  - Syringes discarded in anaesthesiology — 50%
    Weinger MB, J Clin Anesth 2001;13:491-7 (13.50$/case) **10 €/case**

Pharmacoeconomics

Final balance

- **Cost/syringe (€)** **(based on 30'000/year)**

	Pharmacy RTU	Ward
– Investment (5 years)	1.60	
– Development (5 years)	0.40	
– Preparation	3.30	5.10
– Cost-avoiding (safety)		1.80
– Cost-saving (waste)		?
– **Total (first 5 years)**	**5.30**	**6.90**

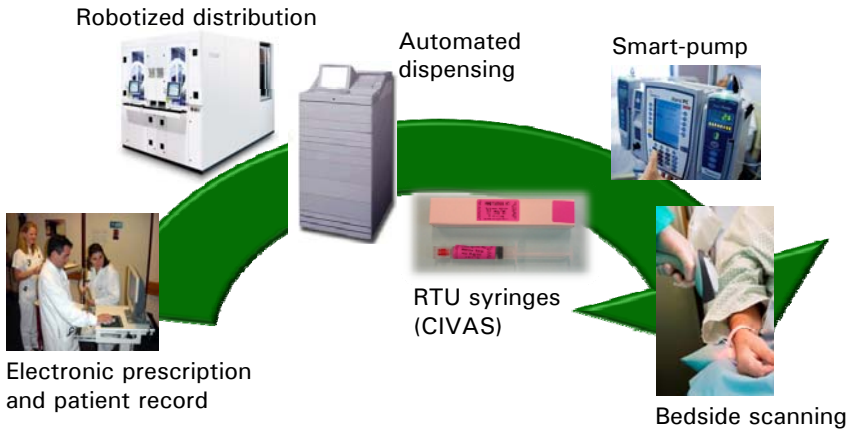
Quality has a cost

« It is difficult to get proofs demonstrating that ready-to-use syringes reduce the frequency of accidents related to dilution errors. However, to standardize practices induces significant cost savings, that can mostly compensate for the overcost of these syringes.

Moreover, hospital directors are more and more sensitive to safety improvement arguments »

Prof. F. Clergue, Head of anaesthesiology, HUG, 2011

Innovations for safety



Computerization **Automation** **Robotisation** **Industrialisation**

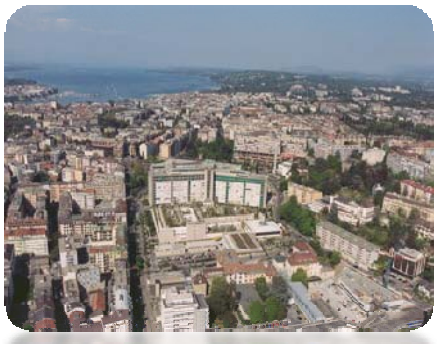
Conclusion

- The preparation of injectables in wards is not reliable (human factors)
- Ready-to-use products improve the chemical and the microbiological safety, by changing the paradigm (industrialisation)
- A high quality assurance system (GMP) is essential to ensure safety
  - Hospital pharmacy level
  - Collaboration with the industry
- The quality has a cost, but it can save money … and lifes !

Thank you for your attention

This presentation can be downloaded

http://pharmacie.hug-ge.ch/ens/conferences.html



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