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Implementation of a CSTD to improve healthcare worker safety and reduced drug waste

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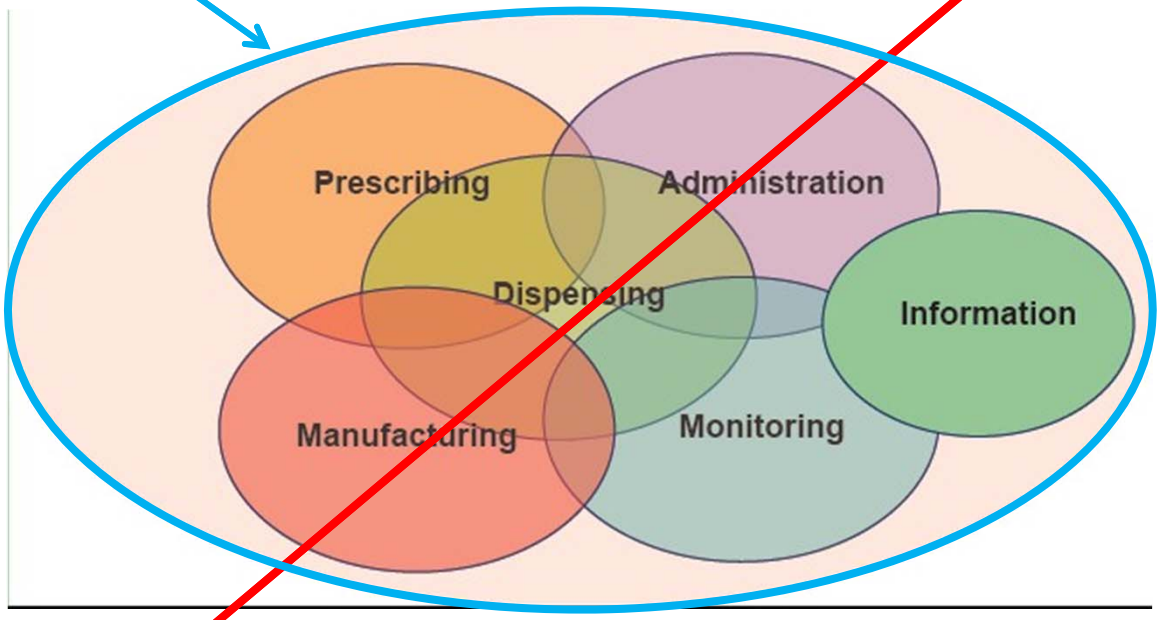
Past President ISOPP

QUALITY = SAFETY

SAFETY FOR THE PATIENT



SAFETY FOR THE STAFF

1. Why Quality ? Chemical - staff

Occupational exposure to cytotoxic drugs is associated with health risks for health care professionals

- As well during preparation as during administration.
- Prevention is possible, protection is needed
- Hierarchic order in prevention / protection
- All routes of contamination into account
- All sources of contamination into account (patient)

Environmental contamination

Uptake in body

Effect on DNA

Effect on pregnancy

Contamination risk

	CHEMO	MAB	NIB
Dermal	+	-	+
Ingestion	+	-	+
Evaporation	+	-	?
Inhalation aerosol	+	+	+
Needlestick injury	+	+	-
Active Transport	-	?	-

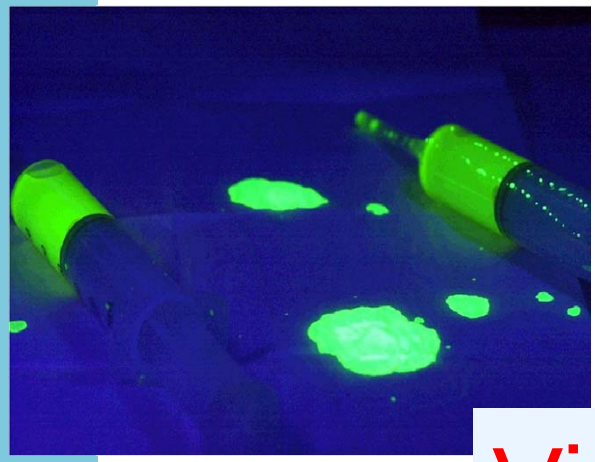
- **External contamination of vials**
  - Production and packaging
- **Drug preparation**
  - Preparation techniques (spills)
- **Drug administration**
  - Administration techniques (spills)
- **Patients excreta**
- **Waste**

Pure product
High conc

1° Dilution

2° Dilution

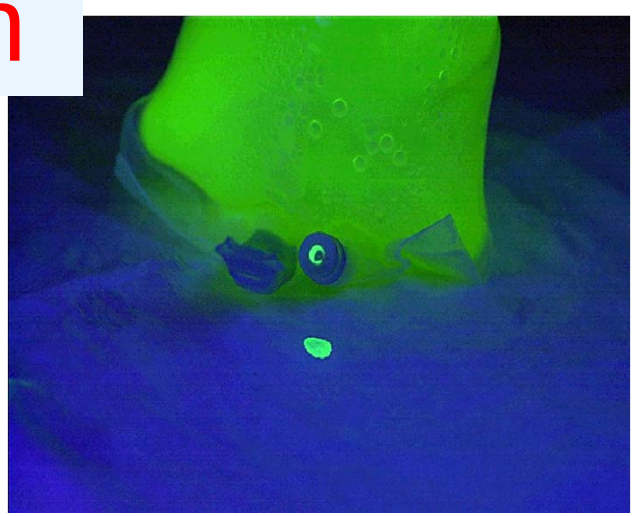
Pure, 1° & 2° Dilution



DRUG RECONSTITUTION WITH NEEDLE AND SYRINGE

Visualisation

DRUG TRANSFER WITH NEEDLE AND SYRINGE



Slides from Tom Connor

Hierarchic order
(European Council Directive 90/394/EEG)

1. **(Replace by a substance not or less dangerous)**
2. **Use closed systems**

1 & 2 = PREVENTION

3. **Evacuation local extraction or general ventilation = BSC, isolators, …**
4. **Individual protection measures = PPE**

3 & 4 = (partial) PROTECTION

NIOSH: Closed System (Drug) Transfer device = CSTD

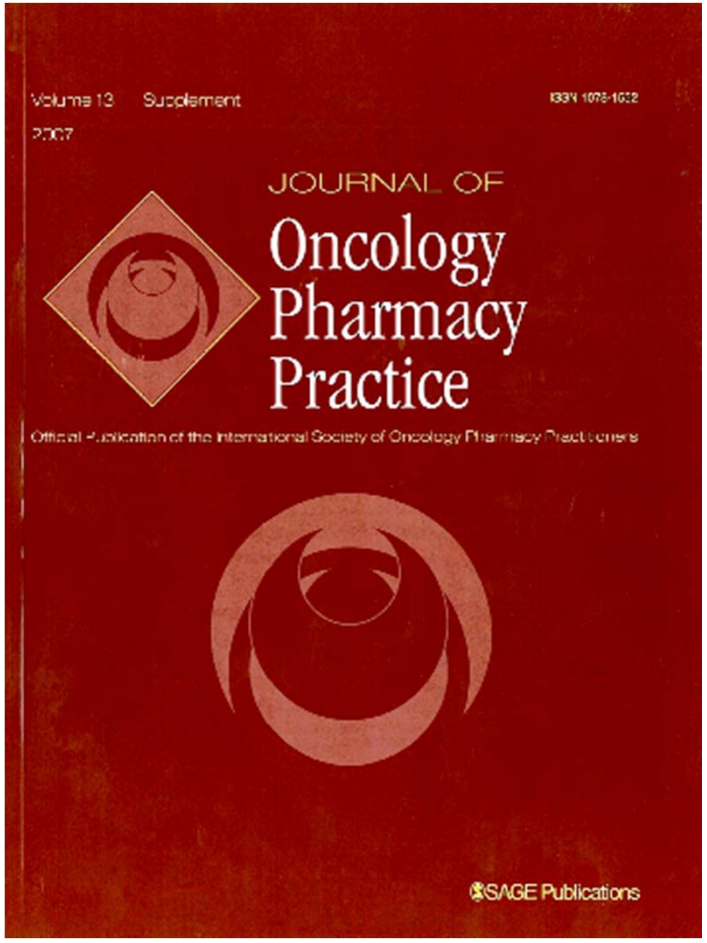
A device that mechanically prohibits

- the transfer of environmental contaminants into the system and
- the escape of hazardous drug or vapour concentrations outside the system

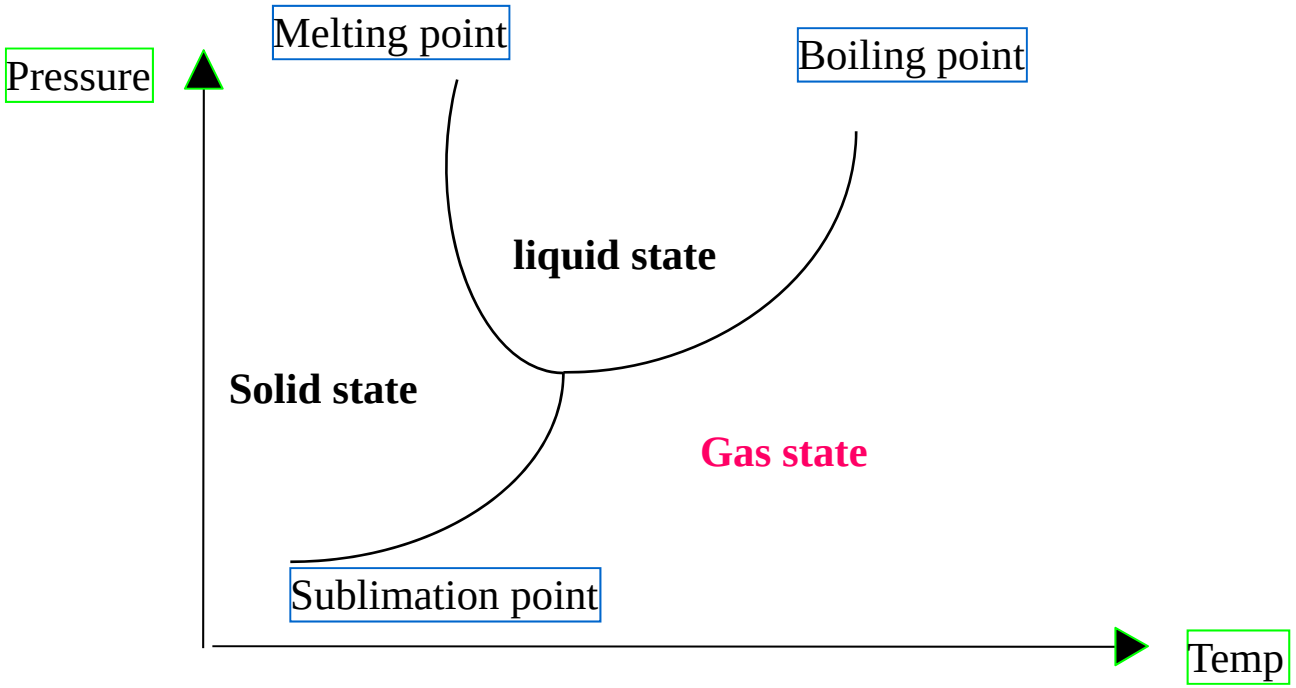
www.cdc.gov/niosh

ISOPP = Air tight & leak proof

USE CLOSED SYSTEMS FOR PREPARATION AND ADMINSTRATION !!


Volume 13 Supplement
2007
JOURNAL OF
Oncology
Pharmacy
Practice
SAGE Publications

Basic research vapour pressure



The presence of a product in gaseous state depends on pressure and temperature.

Possible way out :

- Reduction of human activity ???
- Engineering controls = Enclose the exposure (temporally) ??

It does not help

It gives a false sense of security

WHY ????

THERE IS NO PREVENTION !

Cytotoxic surface contamination during automated compounding

Surface contamination with cytotoxic drug substances 5-fluorouracil and platinum containing drugs was investigated during automated preparation with APOTECAchemo and during manual preparation. The contamination levels during robotic preparation were similar or lower than during manual preparation.

A Benigne, I Krämer – EJOP vol 8, 2014-issue 2 14-17,

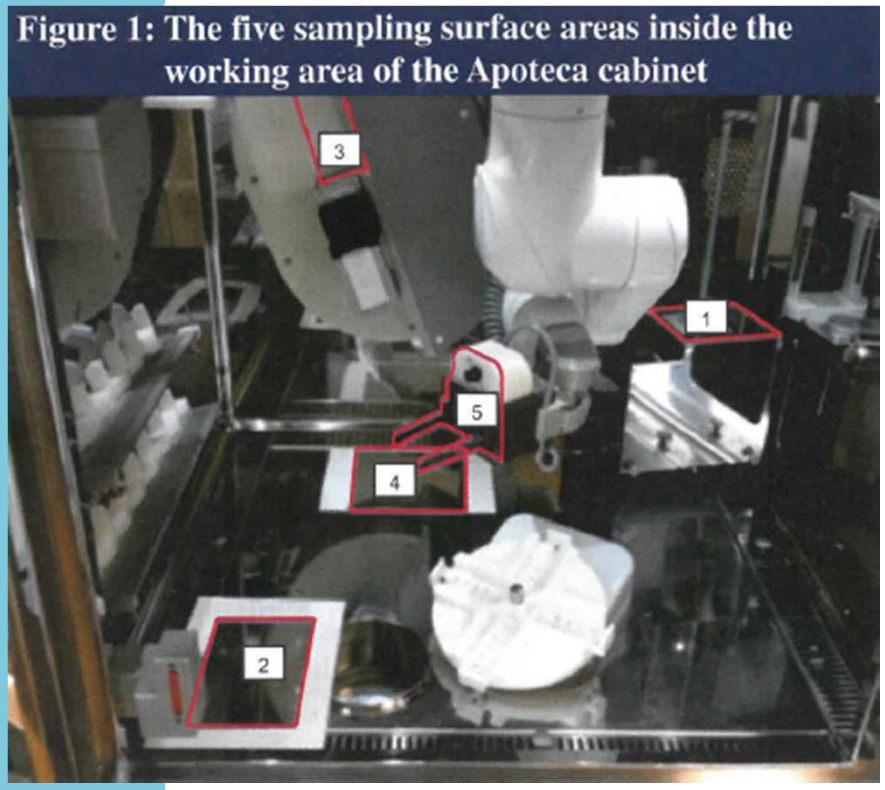


Figure 1: The five sampling surface areas inside the working area of the Apoteca cabinet

compounding		
Place of sampling	5FU (pg/cm²)	Platinum (pg/cm²)
Before compounding		
Balance (ca. 45 cm²)	nn	2,6

Table 2. EPI and 5-FU on isolator surfaces (ng/cm^2) and syringes/gloves/mats (μg)

	Baseline			
Location	EPI		5-FU	
	Batch1	Batch 2	Batch1	Batch 2
Right door (ng/cm^2)	ND	0.05	0.74	2.74
Right floor (ng/cm^2)	ND	0.04	ND	1.27
Right sleeve (ng/cm^2)	0.9	0.09	2.1	3.58
Centre floor (ng/cm^2)	ND	0.04	0.59	1.17
Left sleeve (ng/cm^2)	0.03	0.05	0.39	2.93
Left floor (ng/cm^2)	0.02	0.34	ND	0.77
Left door (ng/cm^2)	ND	0.04	ND	0.70
Gloves/pair[a] (μg)	3.16	7.25	0.85	13.77
Preparation mat[a] (μg)	44.65	38.03	769.90	772.98
Syringe surface:				
% contaminated[b] (N)	57.1 (28)		71.4 (28)	
Total contamination[c] (mean)	0.11 (0.004)		0.74 (3.59)	

ND: not detected.
[a]The values for gloves and preparation mats are total amounts of drug recovered (μg) from e
[b]Percentage of syringes sampled with contamination >LOD (number of syringes in sample).
[c]Total contamination (μg) recovered from samples pooled from both batches (mean contamin

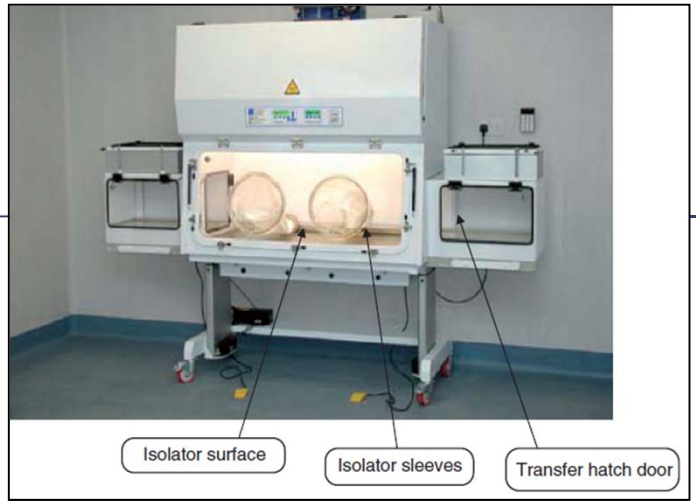
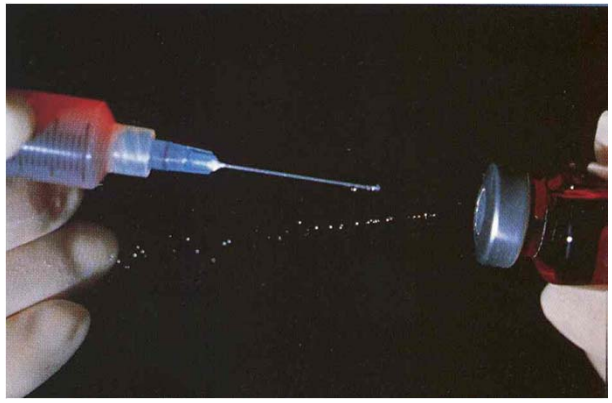


Table 3. Platinum levels recovered from surfaces (ng/cm^2) and gloves/infusion intervention.

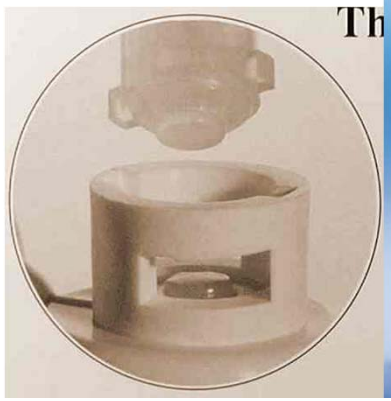
	Platinum (Pt)			
	Baseline			
Location	Batch 1	Batch 2	Batch 3	Batch 4
Right door (ng/cm^2)	0.86	0.18	0.36	0.11

Evaluation of CSTD in a pharmaceutical isolator
Vyas, Turner, Sewell – JOPPP on line July 2014



Microbiologically closed
Physically open

CSTD



Microbiologically closed
Physically closed

ONB – FDA new category

1. No escape of hazardous drug or vapour concentration
2. No transfer of environmental contaminants
3. Prevention of microbial ingress

PhaSeal = first product approved by FDA as ONB

Recognition of safe handling guidelines:

- 3 States in USA passed a law that healthcare facilities must comply with safe handling guidelines of NIOSH (recommends the use of CSTD).
- The current draft of USP Chapter <800> Hazardous Drugs - Handling in Healthcare Settings recommends the use CSTDs during preparation but mandates their use during administration
- Mandatory use of CSTD in Israel
- Mandatory European directive

2. Why Quality ? Microbiology - patient

- **Patients have an compromised immune system by?**
  - chemotherapy,
  - radiation

  Much more need for sterile preparations then for e.g. TPN

- **Wrong conception as if chemo would kill microorganism**
  - Depends on organism
  - Depends on product
  - No short term activity
  - Selected activity on long term

Irene Kramer

Table 2. Viability of *S. aureus* in Drug Solutions and Control Solutions

	Storage temperature (°C)	*S. aureus* (CFU log/ml)									
		0 min	15 min	30 min	60 min	2 h	3 h	4 h	24 h	48 h	120 h
0.9% NaCl	22°C	4.5	4.9	5	4.6	4.7	4.7	4.7	4.5	4.7	4.2
Bendamustin	22°C	4.3	4.6	4.4	4.2	4.4	4.3	3.9	3.2	1.3	0
Cladribine	22°C	4.3	4.0	4.5	4.2	4.2	3.9	3.3	2.4	2.4	0
Fludarabine	22°C	4.4	4.6	4.3	4.5	4.3	4.1	4.1	4.0	4.0	2.5
Foscarnet	22°C	4.2	4.0	4.5	4.6	4.2	4.1	4.1	4.1	4.1	1.9
Ganciclovir	22°C	4.4	4.6	4.3	4.7	4.3	4.1	3.9	1.9	0	0
Idarubicin	22°C	4.4	4.2	4.2	5.0	4.3	4.3	4.2	3.8	2.7	0
Paclitaxel	37°C	4.5	4.5	4.6	4.5	4.6	4.2	4.0	0	0	0
Pentostatin	22°C	4.4	4.6	4.6	4.2	4.2	3.9	3.3	3.2	3.1	0
Treosulfan	37°C	4.3	4.6	4.6	4.5	4.3	3.9	3.1	0	0	0
0.9% NaCl	22°C	4.6	4.8	4.8	4.9	4.9	4.7	4.5	4.7	4.5	4.5
Docetaxel	22°C	4.8	4.8	4.7	4.8	4.8	4.6	4.6	4.1	3.8	0
Gemcitabine	22°C	4.1	4.8	4.8	4.8	4.8	4.6	3.6	1.2	0	0
0.9% NaCl*	37°C	4.5	4.5	4.5	4.6	4.5	4.4	4.3	4.2	0	0
0.9% NaCl*	22°C	4.6	4.5	4.2	4.6	4.5	4.4	4.5	4.2	3.8	0
5% Dextrose*	22°C	4.5	4.4	4.1	4.4	4.4	4.3	4.4	3.5	2.7	0
Oxaliplatin*	22°C	4.5	4.4	4.1	4.6	4.4	4.3	4.7	2.8	0	0
Topotecan*	22°C	4.6	4.5	4.1	4.5	4.3	4.3	4.7	3.9	3.3	0
Vinorelbine*	22°C	4.5	4.5	4.1	4.6	4.4	4.3	4.5	4.0	3.4	0

**CFU = mean of two experiments.*

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Microbial Limit Test

(Antimicrobial preservatives-Effectiveness)

Escherichia coli NCTC 12923
Pseudomonas aeruginosa NCTC 2924
Staphylococcus aureus NCTC 10788
Aspergillus niger NCPF 2275
Candida albicans NCPF 3179

inoculation

Anticancer agents
(each n=1)
Control(NS)
(n=5)
25℃×28Days

A.niger vials : Culture on Sabouraud Agar, 25℃ 3～5Days
Others : Culture on Trypticase Soy Agar, 35℃ 1～2Days

count of the colonies

試験薬剤		微生物	初期添加菌量 (cfu/mL)*3	発育菌量 (cfu/mL)*3	残存率(%)
ラステット®	ETP	*Escherichia coli* NCTC 12923	3.0×10^6	0	0
タキソール®	PTX			0	0
トポテシン®	CPT-11			0	0
ナベルビン®	VNR			0	0
ブリプラチン®	CDDP			0	0
パラプラチン®	CBDCA			0	0
生理食塩液	NS			1.2×10^6	39.7
テット®	ETP	*Pseudomonas aeruginosa* NCTC 12924	3.9×10^7	0	0
ソール®	PTX			0	0
テシン®	CPT-11			3.0 x 10	0.00008
ルビン®	VNR			0	0
プラチン®	CDDP			0	0
プラチン®	CBDCA			0	0
食塩液	NS			2.7×10^7	69.7
テット®	ETP	*Staphylococcus aureus* NCTC 10788	5.2×10^6	0	0
ソール®	PTX			0	0
テシン®	CPT-11			0	0
ルビン®	VNR			0	0
プラチン®	CDDP			0	0
プラチン®	CBDCA			0	0
食塩液	NS			5.3×10^3	0.1
テット®	ETP	*Aspergillus niger* NCPF 2275	1.7×10^5	0	0
ソール®	PTX			0	0
テシン®	CPT-11			1.2×10^3	0.7
ナベルビン®	VNR			$1.0 \times 10^{2*1}$	0.06
ブリプラチン®	CDDP			5.5×10^2	0.3
パラプラチン®	CBDCA			0	0

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Microbiological challenge of four protective devices for the reconstitution of cytotoxic agents

De Prijck, D'Haese, Vandenbroucke

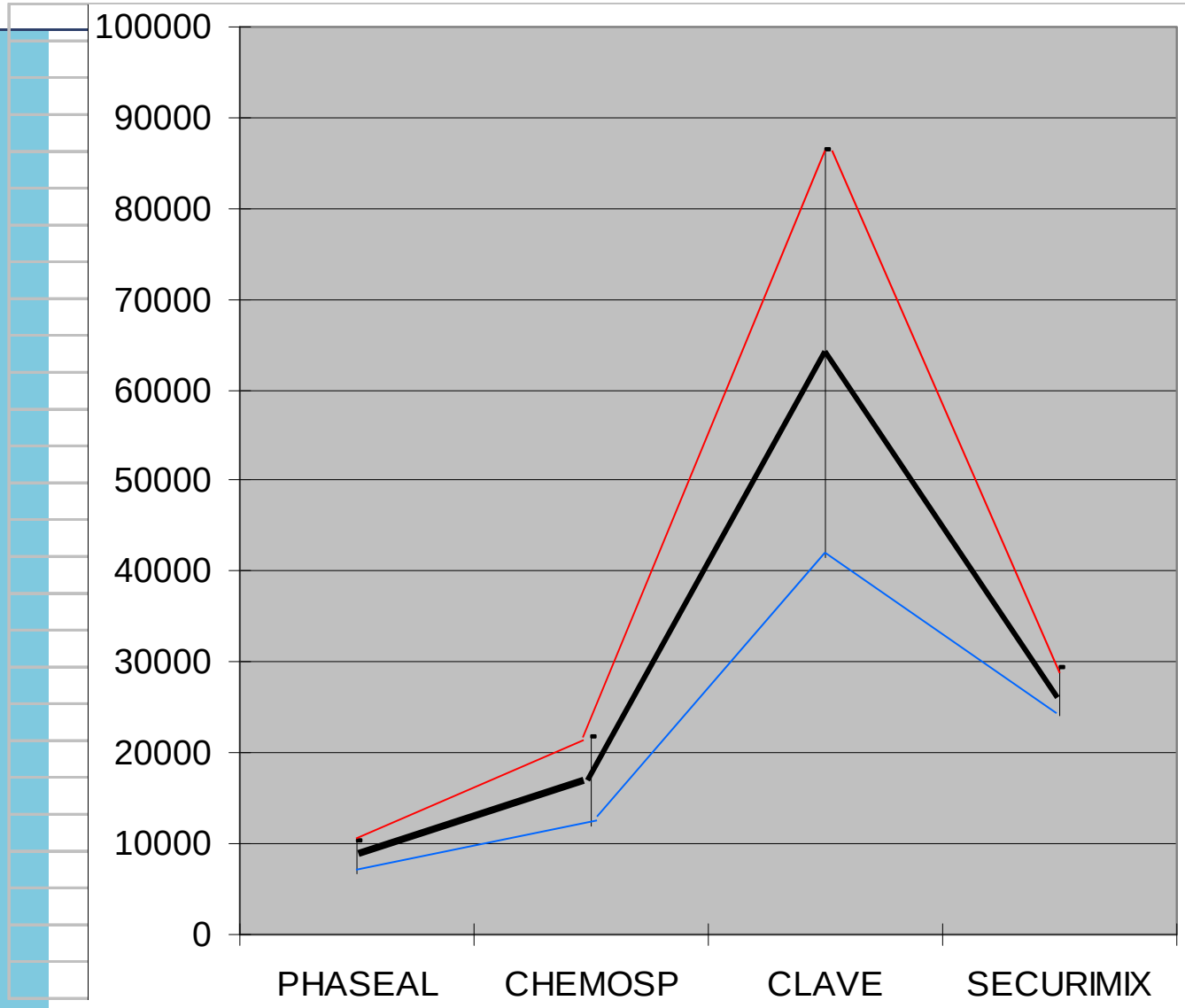
CONTAMINATION OF VIAL DOP

- PSEUDOMONAS AEROGINOSA

➔ 4×10^3 (= R.C.)

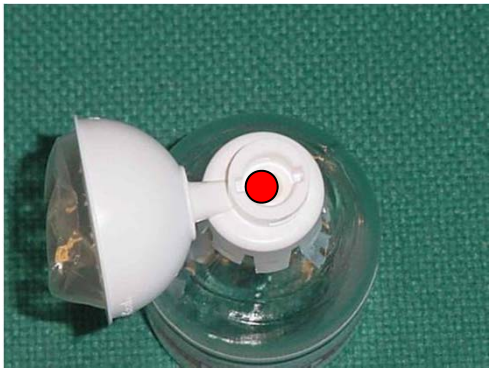
➔ 4×10^5 (= W.C.)

WORST CASE SCENARIO



Need for good decontamination protocol

CONTAMINATION OF TRANSFER DEVICE with Pseud.Aer.



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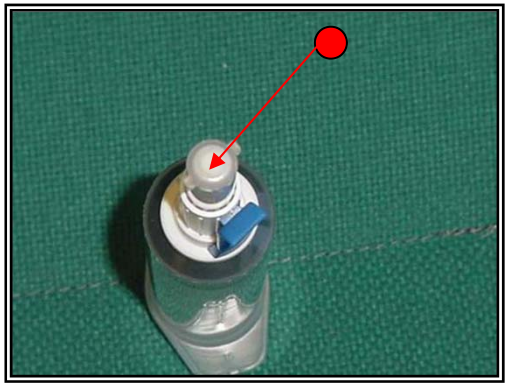
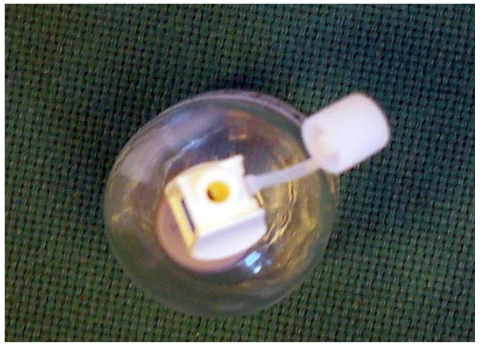
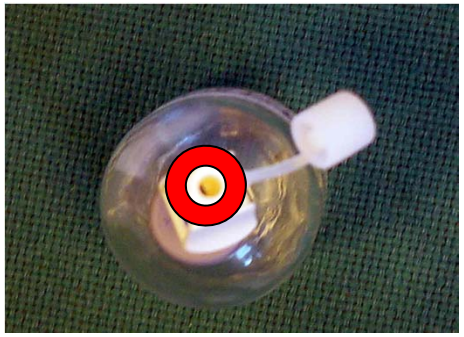
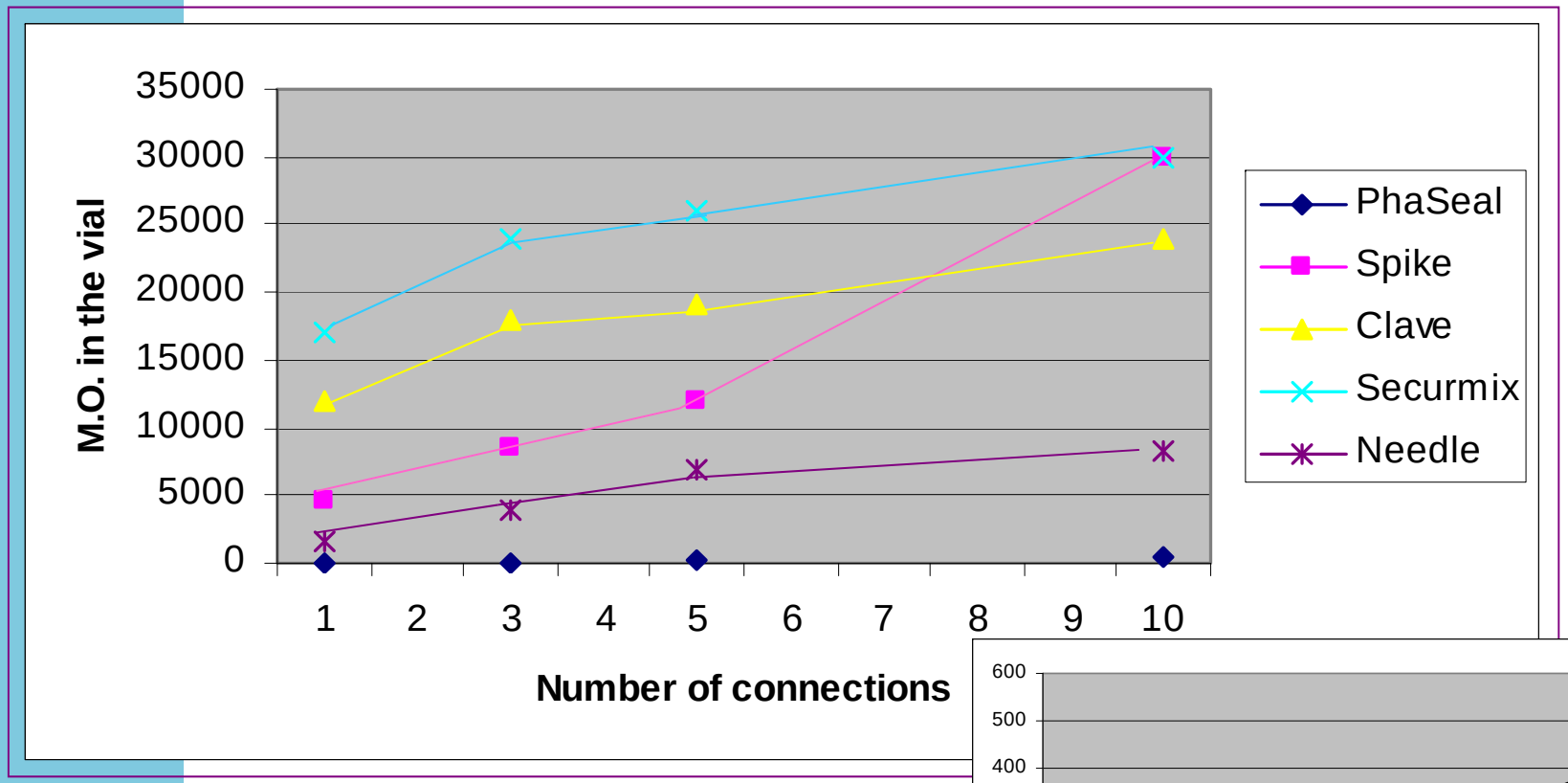


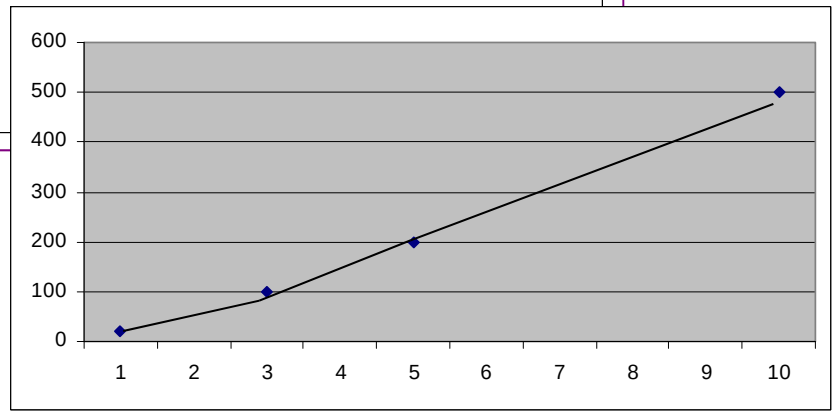




RESULTS MULTIPLE CONNECTIONS (N = 10) W.C.



PhaSeal



Microbial integrity test - Wickham Lab UK

- **Procedure:**

  24 Vials with growth medium (20T + 2P + 2N)

  PhaSeal use in class B conditions

  5 activations / vial

  Whole immersion of inverted vials in E coli susp for 30 minutes

  Incubation for 14 days at 30 -35 °C

- **Results:**

  20 Test vials = all negative

  2 positive test vials = all positive

  2 negative test vials = all negative

Second Look at Utilization of a CSTD

E. Thomas Carey Am J Pharm benefits 2011; 3: 311- 318

The 1°objective was to assess the ability of the PhaSeal system to maintain product sterility given current USP <797> and ISO guidelines for use.

- At the 168-hour mark, there was a probability of failure of 0.3%.
- In other words, there is a **99.7%** probability that the vial would not be contaminated with bacterial growth if the same procedures were utilized under the same environmental conditions

The 2° objective was to determine whether the vials could be used over an extended period of time while maintaining sterility.

- This study demonstrates the CSTDs utility in expanding shelf life
- Therefore reducing waste of viable pharmaceuticals.

3. Cost reduction ?

If product meets ONB criteria ➔

Use for longer period according to

- Chemical and Physical stability
- National / local guidelines (7 days USA)
- In situ situation of infrastructure
- Acceptance of responsible Pharmacist

➔ **Save costly medication (increase income)**

➔ **Reduced waste** (High incineration cost**)**

➔ **Save essential medication** (drug shortage)

Economical impact of the preparation scenario for cytotoxic drugs: an observational study

Vandenbroucke, Robays – UZ Gent / Belgium

www.ejhp.eu

EJHP Practice

European Journal of Hospital Pharmacy Practice

Official Journal of the European Association of Hospital Pharmacists (EAHP)

2008, volume 14; issue 5

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	scenario 1				scenario 2				scenario 3		
	dose/patient	vials used	reimbursment		dose/day	vials used	reimbursment		dose/day	vials used	reimbursment
day 1	187 mg	1 X 100	1 X 100		625 mg	6 X 100	1 X 100		625 mg	7 X 100	1 X 100
		1 X 50	1 X 50			3X10	1 X 50				1 X 50
		4 X 10	4 X 10				4 X 10				4 X 10
	235 mg	2 X 100	2 X 100				2 X 100				2 X 100
		4 X 10	4 X 10				4 X 10				4 X 10
	203 mg	2 X 100	2 X 100				2 X 100				2 X 100
		1 X 10	1 X 10				1 X 10				1 X 10
day 2	202 mg	2 X 100	2 X 100		343 mg	3 X 100	2 X 100		343 mg	3 X 100	2 X 100
		1 X 10	1 X 10			1 X 50	1 X 10				1 X 10
	141 mg	1 X 100	1 X 100				1 X 100				1 X 100
		1 X 50	1 X 50				1 X 50				1 X 50
	total	8 X 100	8 X 100		total	9 X 100	8 X 100		total	10 X 100	8 X 100
		2 X 50	2 X 50			1 X 50	2 X 50		32 mg recup next day		2 X 50
		10 X 10	10 X 10			3 X 10	10 X 10				10 X 10
	mg needed		968		mg needed		968		mg needed		968
	mg used		**1000**		**mg used**		**980**		**mg used**		**968**
	drug waste		**32**		**drug waste**		**12**		**drug waste**		**0**
	mg reimbursed		1000		mg reimbursed		1000		mg reimbursed		1000
	Nr vials used		**20**		**Nr vials used**		**13**		**Nr vials used**		**10**

- In total **3086** preparations are evaluated.
- In the observation period, **39 different products** were used with a top 10 of most used products :

product	number of preparations
FLUOROURACIL	718
CYCLOPHOSPHAMIDE	229
ETOPOSIDE	182
CISPLATINE	178
DOXORUBICINE	177
CYTARABINE	166
GEMCITABINE	151
VINCRISTINE	133
OXALIPLATINE	116
IRINOTECAN	103

Remark : No Mab's in top 10 at that time

Results : Total cost difference

Table 6	Scenario 1	Scenario 2	Scenario 3
product	836198	785079	738329
protector	36214	22230	16113
total	872412	807309	754442
Difference with scenario 3 (Euro)	117970	52867	
Difference in % with scenario 3	+ 15,6%	+ 7,0 %	

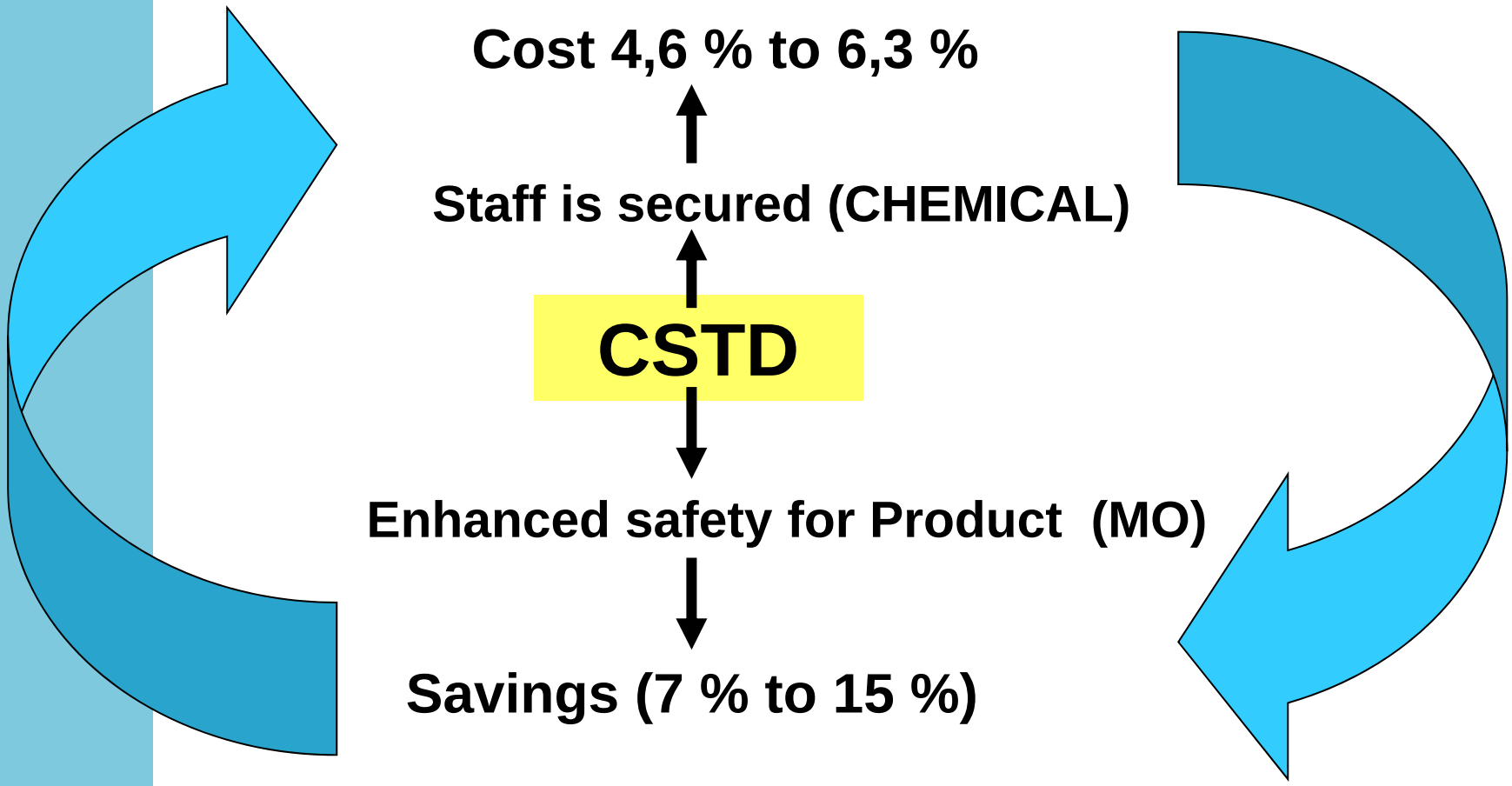
% costs due to CSTD (PhaSeal)

	Scenario 1	Scenario 2	Scenario 3
CSTD	€54,668	€40,684	€34,567
	6,3%	5,0 %	4,6 %

➔ **MINIMUM CSTD Cost = 4.6% OF DRUG COST**

➔ **MAXIMUM CSTD COST = 6.3% OF DRUG COST**

What is the cost of safety ?



Economics – beyond use extension
Rowe, Savage, Eckel - UNC Health Care

Methodology, cont.

Product	Strength (mg)	Disp Date & Time	Time B/w Doses	0:00	6:00	24:00	36:00	48:00	72:00
bevacizumab	750	3/2/09 2:53 PM	9:42:00	50	50	50	50	50	50
bevacizumab	250	3/3/09 12:35 AM	9:41:00	150	150	0	0	0	0
bevacizumab	1335	3/3/09 10:16 AM	23:38:00	65	65	65	65	65	65
bevacizumab	869	3/4/09 9:54 AM	2:34:00	31	31	96	96	96	96
bevacizumab	700	3/4/09 12:28 PM	1:08:00	100	131	196	196	196	196
bevacizumab	420	3/4/09 1:36 PM	21:06:00	80	111	176	176	176	176
bevacizumab	640	3/5/09 10:42 AM	2:34:00	160	160	36	36	36	36
bevacizumab	770	3/5/09 1:36 PM	2:55:00	30	190	66	66	66	66
bevacizumab	450	3/5/09 4:31 PM	19:01:00	50	140	16	16	16	16
bevacizumab	574	3/6/09 11:32 AM	73:13:00	26	226	42	42	42	42

Vial size = 400 mg and 100 mg

Total Hazardous Drug Waste (%)

	0 hours	6 hours	24 hours	36 hours	48 hours	72 hours
alemtuzumab	23.00%	23.00%	16.00%	7.67%	7.67%	7.67%
bevacizumab	8.62%	6.23%	1.18%	0.64%	0.64%	0.31%
bleomycin	34.05%	31.60%	23.00%	23.00%	23.00%	23.00%
bortezomib	36.89%	27.09%	11.90%	8.07%	8.07%	8.07%
busulfan	6.94%	6.94%	6.94%	4.67%	4.67%	4.67%
cyclophosphamide	33.40%	9.75%	1.95%	1.64%	1.03%	0.10%
cytarabine	62.83%	26.84%	8.84%	5.08%	5.08%	1.83%
docetaxel	14.21%	3.45%	0.44%	0.44%	0.44%	0.29%
gemcitabine	12.21%	3.00%	0.43%	0.35%	0.17%	0.13%
ifosfamide	31.50%	28.24%	19.04%	14.67%	12.50%	9.79%
infliximab	1.39%	1.39%	1.23%	0.46%	0.46%	0.15%
irinotecan	10.81%	7.38%	3.35%	3.03%	2.70%	1.38%
methotrexate (pf)	34.84%	16.83%	11.56%	9.47%	8.93%	7.56%
oxaliplatin	12.42%	6.65%	2.46%	1.58%	1.58%	1.28%
pemetrexed	17.13%	11.60%	10.41%	10.41%	9.18%	5.29%
rituximab	11.70%	4.05%	0.82%	0.51%	0.27%	0.19%
topotecan	40.63%	22.40%	10.94%	7.80%	5.58%	3.24%
vinCRIStine	14.58%	4.48%	1.20%	0.99%	0.56%	0.13%
vinorelbine	11.07%	11.07%	11.07%	10.17%	10.17%	10.17%

Economic and Microbiologic Evaluation of Single-Dose Vial Extension for Hazardous Drugs

Erinn C. Rowe, JOPP 2012; 4, 45-49

- **Waste associated with implementation of the USP <797> SDV 6-hour BUD recommendation is substantial and our waste log reiterates this with an annual cost of $770,888.**

- **The evaluation of extending vial life beyond 6 hours was demonstrated with a microbiologic study (up to 14 days).**

Cost saving realized by PhaSeal

- **Edwards, Solimando & all - JOPP 2013; 0: 1-10**

- **Study:**

  25 drugs with minima 48 H stability

  296 vials used in 50 days period

  Mean potential % of drug waste = 57%

- **Results:**

  Actual saving in test period = $96,348

  Yearly drug saving = $703,047

  Yearly cost PhaSeal = $106,556

5. Conclusion

A CSTD – ONB approved product can assure

Security for the staff
Security for the environment
Security for the product – particulate contamination
Security for the product – microbial contamination
Reduction of medication cost
Reduction of waste cost
Saving essential medication in case of drug shortage