Evaluating the Use of Closed System Transfer Devices (CSTDs) in Aseptic Services

Louisa Knowles

Advanced Pharmacist for Technical Services

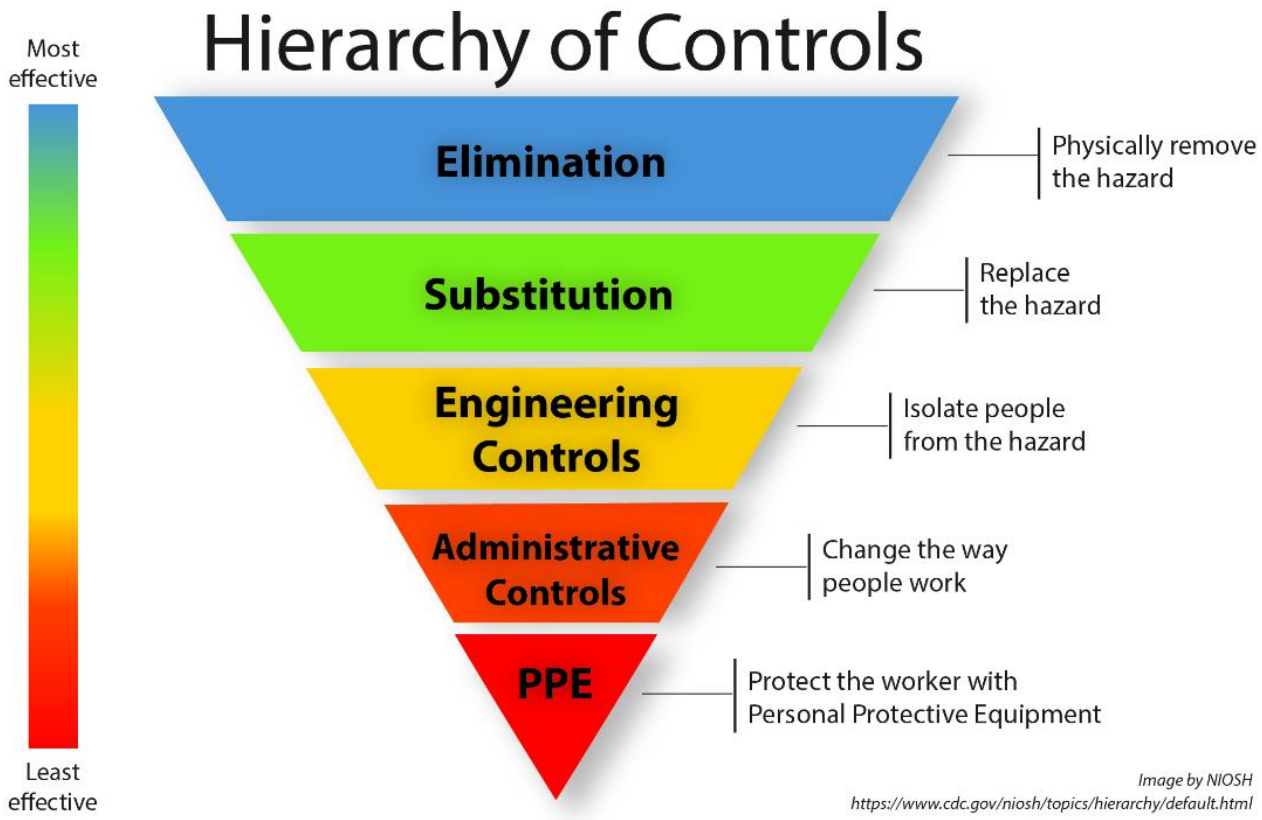
Introduction

Cytotoxic Drugs for the Treatment of Cancer

- Mutagenic
- Carcinogenic
- Teratogenic

Skin absorption	Inhalation	Ingestion	Needle Stick Injuries

Introduction to Guidance/Legislation



- Directive 2004/37/EC the protection of workers from the risks related to exposure to carcinogens or mutagens at work
- European Biosafety Network – Amendments to the Carcinogens and Mutagens Directive
- HSE – Control of Substances Hazardous to Health Regulations (UK).
- HSE – Safe Handling of Cytotoxic Drugs in the Workplace
- ISOPP – Standards for the Safe Handling of Cytotoxics
- NIOSH – Preventing Occupational Exposures to Antineoplastic and other Hazardous Drugs in Health Care Settings
- USP – General Chapter 800 Hazardous Drugs Handling in Healthcare Settings

Introduction to CSTDs

<0.1ng/cm²

Evidence for CSTDs

- Reduced cytotoxic contamination in preparation and administration areas
- Reduced cytotoxic levels in the urine of workers

- Cochrane Review, 2018 (1)
  - 24 studies
  - Lack of evidence
  - Low quality
  - High risk of bias
  - Largely industry sponsored

CSTD Syringe Caps for IV Bolus Administration

- NHS Pharmaceutical Quality Assurance Committee (2)
  - CSTD caps with syringes for intravenous use
  - Attached immediately prior to administration
- Syringe integrity testing on Tevadaptor® (3)
  - Microbiological and physical challenges
  - Compliant with the "Protocols for the Integrity Testing of Syringes" (4)
- Stability and compatibility testing on Tevadaptor® (5)
  - Compliant with "Standard Protocol for Deriving and Assessment of Stability" (6)
  - 11 drugs then Interpolation with other drugs (7)
- Use of a closed-system drug transfer device reduces contamination with doxorubicin during bolus injection, 2020 (8)

MSc Research Project

Aim

To determine if the addition of a CSTD syringe adaptor in the isolator reduces cytotoxic residue contamination during intravenous bolus administration.

Objectives

1. To confirm the syringe integrity of the Tevadaptor® Syringe Adaptor Lock attached to a luer-lock syringe.

2. To quantify the level of cyclophosphamide contamination during intravenous bolus administration via a luer-lock syringe with a standard syringe hub cap.

3. To quantify the level of cyclophosphamide contamination during intravenous bolus administration via a luer-lock syringe with a Tevadaptor® Syringe Adaptor Lock.

Method – Syringe Integrity Testing

Syringe Size (ml)	Volume of Broth (ml)	Quantity Prepared
1ml	0.85ml	3
3ml	2.5ml	3
5ml	4.2ml	3
10ml	8.4ml	3
20ml	17ml	3
30ml	25ml	3
50ml	50ml	3

- Aseptic preparation
- Stored for 7 days
- Sent to QCNW
- Incubated
- Liquid media fertility testing
  - S.aureus, C.albicans, B.subtilis, A.brasiliensis, Cl.sporogenes, P.aerginosa
- Quality Assurance of Aseptic Preparation Services (9)
- Protocols for the Integrity Testing of Syringes Guidance (4)
- End of Session Broth Fill Technique (10)

Method – Cyclophosphamide Syringe Preparation

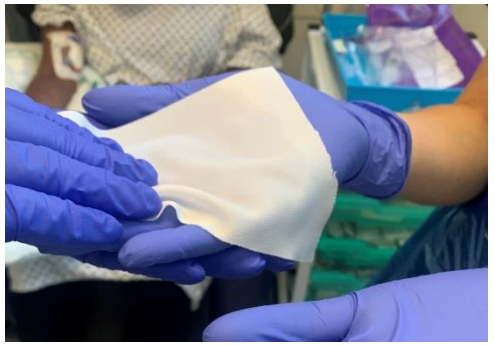
Cyclophosphamide Syringes Prepared with a Standard Syringe Hub Cap		
Dose (mg)	Volume (ml)	Quantity
1000mg	50ml	1
800mg	40ml	1
700mg	35ml	2
600mg	30ml	2
500mg	25ml	3
400mg	20ml	4
300mg	15ml	4
200mg	10ml	4
100mg	5ml	4

Cyclophosphamide Syringes Prepared with a Tevadaptor® Syringe Lock		
Dose (mg)	Volume (ml)	Quantity
800mg	40ml	2
700mg	35ml	1
600mg	30ml	4
500mg	25ml	5
400mg	20ml	2
300mg	15ml	4
200mg	10ml	5
100mg	5ml	2

- Aseptic preparation
- Negative pressure isolator
- Tevadaptor® syringe adaptor locks

Method – Cyclophosphamide Syringe Sampling

- Fresh nitrile gloves
- 3 sampling points per syringe
  - Surface of syringe/cap
  - Connect/disconnect
  - Nurses' gloves
- Positive control
- Negative control



Method – Cyclophosphamide Syringe Analysis

- 10ml of 50% MeOH
- Roller
- 93.4% recovery
- 4µl injected into the LC-MS machine.
- Positive control
- Negative control
- LOD = 7pg/cm^2

Statistical Analysis

- Mann-Whitney U Test
- Null hypothesis 1 = There is no significant difference between the level of cyclophosphamide contamination on the syringes, between syringes with a standard hub cap and syringes with a Tevadaptor® cap.
- Null hypothesis 2 = There is no significant difference between the level of cyclophosphamide contamination on the swabs used for connect/disconnect, between syringes with a standard hub cap and syringes with a Tevadaptor® cap.
- Null hypothesis 3 = There is no significant difference between the level of cyclophosphamide contamination on the nurses' gloves, between syringes with a standard hub cap and syringes with a Tevadaptor® cap.

Results – Syringe Integrity Testing

Passed the syringe integrity testing validation

None of the broth filled syringes grew any microbial contamination

Fertility tests yielded growth of the requested microorganisms, except Cl.sporogenes.

Results – Cyclophosphamide Contamination on Syringes

A significant reduction in contamination when Tevadaptor® caps were used (Mdn = 0.62) compared to standard hub caps (Mdn = 8.29), $z = 3.597$, $p < 0.001$ with a confidence interval of 95%.

Null hypothesis 1 was therefore rejected.

Samples above European Biosafety Network recommended limit of $<0.1 ng/cm^2$

- 12 with the standard syringe hub cap
- 0 with the Tevadaptor® cap

Results – Cyclophosphamide Contamination on Connect/Disconnect

A significant reduction in contamination was observed when Tevadaptor® caps were used (Mdn = 0.00) compared to standard hub caps (Mdn = 384.82), z = 5.801, p <0.001 with a confidence interval of 95%.

Null hypothesis 2 was therefore rejected

Samples above European Biosafety Network recommended limit of <0.1ng/cm^2:

- 19 with the standard syringe hub cap
- 0 with the Tevadaptor® cap

Results – Cyclophosphamide Contamination on Nurses' Gloves

A significant reduction in contamination was observed when Tevadaptor® caps were used (Mdn = 0.00) compared to standard hub caps (Mdn = 1.11), $z = 5.904$, $p < 0.001$ with a confidence interval of 95%.

Null hypothesis 3 was therefore rejected.

Samples above European Biosafety Network recommended limit of $<0.1 ng/cm^2$:

- 2 with the standard syringe hub cap
- 0 with the Tevadaptor® cap

Results – Positive and Negative Controls

	Cyclophosphamide Contamination (ng)
Positive Control 1 – Standard Syringe Hub Cap	30730.12
Positive Control 2 – Tevadaptor® Syringe Adaptor Lock	4922.23

	Cyclophosphamide Contamination (ng)
Negative Control 1 – Standard Syringe Hub Cap	<LOD
Negative Control 2 – Tevadaptor® Syringe Adaptor Lock	<LOD

Discussion

Addition of the Tevadaptor® caps to syringes in the isolator significantly reduced cytotoxic residue on IV administration

Reduce risk of mutagenic, carcinogenic and teratogenic events

Reduced standard deviation with Tevadaptor® caps
Less variability due to removal of human factor

Beneficial to add in the aseptic unit compared to ward level
Significant reduction on nurses' gloves

Syringe integrity replicated with in-house processes

Limitations of the Study

Nurses' gloves

Tevadaptor®

UHB Aseptic Unit

Positive Controls

Future Work

- Other CSTDs
- Full CSTD Device
- Other Final Containers
- Pharmacy Setting
- Extended Shelf Life

Further Considerations

- Other CSTDs
- Cost
- Triple wrapped
- Commercial units

Conclusion

The addition of a CSTD syringe adaptor in the isolator reduces cytotoxic contamination during IV bolus administration

Further research needs to be completed

Further considerations need to be taken into account

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