Implementing ISOPP standards

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ISOPP GOLDEN STANDARD
= guideline which harmonizes technical
with clinical oncology pharmacy

INDEX ISOPP Standard
1. Introduction and Definitions
2. Transport
3. Personnel
4. Education and Training
5. Hierarchic order in protection measures
6. Facilities for sterile cytotoxic reconstitution
   and personal protective equipment
7. Special Devices
8. Ventilation Tools
9. Non sterile preparations
10. Chemical contamination monitoring
11. Checking procedures
12. Administration of cytotoxic drugs
13. Cleaning procedures
14. Cytotoxic spills, extravasations and other
   incidents
15. Waste handling and patient excreta
16. Laundry
17. Warning staff of presence of cytotoxic agents
18. Home care
19. Risk management
20. Medicines management
21. Documentation
ISOPP standard

- Is a HIGH standard
- Is something to work towards
- Takes time to implement
- Takes time to complete
- Has only 2 goals, 1. To improve quality 2. To improve safety

SAFETY FOR THE STAFF

What do we know from patient data?

Adverse effects of cytotoxics

- Classical cytotoxics are **not tumour specific**:
  and may therefore damage growth and reproduction of normal cells as well.
- Effects are
  - Product and dose related
- Effect on:
  - Bone marrow (suppression), Gastro-intestinal (vomiting/diarrhea), hair loss
  - Secondary malignity's (5% of all patients)
  - Gonades: oligospermy, sterility, teratogenicity

What about health professionals?
### Summary of Studies of Adverse Reproductive Outcomes in Workers Exposed to Antineoplastic Drugs

<table>
<thead>
<tr>
<th>Year</th>
<th>Author</th>
<th>Population</th>
<th>Birth Defect</th>
<th>Fetal Loss</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>1992</td>
<td>Skov</td>
<td>Onc Nurses</td>
<td>+</td>
<td>-</td>
<td>Ecopic preg.</td>
</tr>
<tr>
<td>1993</td>
<td>Stucker</td>
<td>Onc Nurses</td>
<td>+</td>
<td>LBW, - SGA</td>
<td>Ecopic preg.</td>
</tr>
<tr>
<td>1993</td>
<td>Saurel-Cubizolles</td>
<td>OR/Nurses</td>
<td>* Ectopic preg.</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>1995</td>
<td>Shortridge</td>
<td>Onc Nurses</td>
<td>* Menstrual dysf.</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>1997</td>
<td>Valanis</td>
<td>Pharm + RNs</td>
<td>* Infertility (F); + (M)</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>1999</td>
<td>Valanis</td>
<td>RN, Pharm (M+F)</td>
<td>* (F); + (M)</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>1999</td>
<td>Peelen</td>
<td>Onc Nurses/Prep</td>
<td>-/+ LBW</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

Source: Melissa McDiarmid; University of Maryland

### IARC List
- 5 commonly used cytotoxic drugs are listed in group I, “proven carcinogenic”
  - (e.g. cyclophosphamide, etoposide (comb), alkylating agents, …)
- 4 commonly used cytotoxic drugs are listed in group II A “probably carcinogenic”
  - (e.g. adriamycine, cisplatinum, etoposide, tenoposide.)
- 5 commonly used cytotoxic drugs are listed in group II B “possible carcinogenic”
  - (e.g. bleomycine, dacarbazline, mitomycine, …)

### Incidence of Cancer among Nurses Handling Antineoplastic Drugs in Oncology Departments

<table>
<thead>
<tr>
<th>Site</th>
<th>OBS</th>
<th>EXP</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All malignant neoplasms (ICD-7 140-205)</td>
<td>14</td>
<td>11.69</td>
<td>1.20 (0.65-2.01)</td>
</tr>
<tr>
<td>Lymphatic and haematopoietic issues (ICD-7 200-205)</td>
<td>3</td>
<td>0.56</td>
<td>5.37 (1.11-15.7)</td>
</tr>
<tr>
<td>NHL (ICD-7 200, 202)</td>
<td>0</td>
<td>0.20</td>
<td>-</td>
</tr>
<tr>
<td>Hodgkin’s disease (ICD-7 201)</td>
<td>1</td>
<td>0.12</td>
<td>8.35 (0.21-46.5)</td>
</tr>
<tr>
<td>Multiple myeloma (ICD-7 203)</td>
<td>0</td>
<td>0.05</td>
<td>-</td>
</tr>
<tr>
<td>Leukemia (ICD-7 204)</td>
<td>2</td>
<td>0.19</td>
<td>10.65 (1.29-38.5)</td>
</tr>
<tr>
<td>Mycosis fungoides (ICD-7 205)</td>
<td>0</td>
<td>0.01</td>
<td>-</td>
</tr>
</tbody>
</table>


### Genotoxicity Assessment in Oncology Nurses Handling Antineoplastic Drugs

Rekhadevi, Sailaja, Chandrasekhar

- Urinary cyclophosphamide used as marker for drug absorption was measured in the urine of the nurses.
- DNA damage observed in lymphocytes of exposed nurses was significantly higher than the controls.
- Similarly, a significant increase in micronuclei (MN) frequency with peripheral blood lymphocytes and buccal cells was observed in exposed nurses compared to controls (P<0.05).
- Multiple regression analysis showed that occupational exposure and age had a significant effect on mean comet tail length as well as on frequency of MN.
Sources of contamination
§ External contamination of drug vials
   Production and packaging
§ Drug preparation
   Preparation techniques (spills – leakage)
§ Drug administration
   Administration techniques (spills - leakage)
§ Patient excreta
§ Waste

Research of Opiolka and Schmidt

Risk Analysis 2
△ Biological effect monitoring (BEM)
   Ames test
   Chromosomal aberrations (CA)
   Sister chromatid exchanges (SCE)
△ Environmental Monitoring (EM)
   Measures the presence/release of the drug in the environment
△ Biological Monitoring (BM)
   Assessment of uptake of the drug in the body of the worker
   Estimation of health-risk for the worker

Surface contamination with cyclophosphamide in preparation areas (ng/cm²)

<table>
<thead>
<tr>
<th>Description surface</th>
<th>Canada</th>
<th>USA</th>
<th>Belgium</th>
<th>Sweden</th>
<th>Germany</th>
<th>Netherlands</th>
</tr>
</thead>
<tbody>
<tr>
<td>Table top preparation ESSC</td>
<td>0.01-2.63</td>
<td>0.08-3.03</td>
<td>0.13-5.81</td>
<td>4.74-15.22</td>
<td>14.02-14.22</td>
<td>0.01-1.16</td>
</tr>
<tr>
<td>Floor under ESSC</td>
<td>0.05-0.32</td>
<td>0.03-2.40</td>
<td>0.05-0.55</td>
<td>1.79</td>
<td>0.05</td>
<td>0.01-0.03</td>
</tr>
<tr>
<td>Floor central preparation room</td>
<td>0.11-0.16</td>
<td>0.01-2.36</td>
<td>0.15-0.31</td>
<td>1.34</td>
<td>1.77</td>
<td>0.01-0.02</td>
</tr>
<tr>
<td>Table top not for cyclopreparation</td>
<td>0.02</td>
<td>0.01-0.19</td>
<td>0.01-0.36</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Floor entrance preparation room</td>
<td>0.52</td>
<td>0.16</td>
<td>0.01-0.02</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Floor entrance preparation room cleaner</td>
<td>0.01-0.13</td>
<td>0.14-0.19</td>
<td>0.09</td>
<td>0.01</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data from exposure control, NL
Data from exposure control

### ISOPP recommendation
- Wipe sampling & urine sampling not in routine
- Useful in context of project
- Willing to react

### Risk Analysis 3

§ Easy and cheap method of visualization
- Using Fluorescence dye
- Using Quinine
  - And UV Light

### Staff

EXCLUSION FROM ACTIVITIES
- PREGNANCY
- REMOVED DIRECT ACTIVITY
- APPOINTED ANOTHER WARD
- FAMILY PLANNING ????
- REMOVED DIRECT ACTIVITY
- MALE + FEMALE

### Responsibility of the Pharmaceutical Company

- To deliver to the customer contamination-free drug containers.
- Certification of the contamination-free drug containers is strongly advised.
Facilities

- Centralised (pharmacy or satellite)
- Separate room
- Pressure difference (-)

Hierarchic Order in Protection

1. REPLACEMENT
2. CLOSED SYSTEM
3. LOCAL AND GENERAL VENTILATION/EXTRACTION
4. PERSONAL PROTECTION TOOL

Most of the guidelines mention only level 4

European council directive

Level 4 protection

- Personal protection
  - Also for non-preparing staff (warehouse, waste)
- Proof of resistance
  - Static tests
  - Dynamic tests
- Education and training

Ventilation Tools = level 3

Closed Systems = level 2 protection

NIOSH

Closed system drug-transfer device = 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

Why isolator & BSC ???

- To prevent from microbiological contamination
- To protect the product
- We have adapted the system for other purposes
- To prevent from chemical contamination
- To protect the manipulator
- BUT IT DOES NOT WORK because they DO NOT PREVENT
What can the patient expect?

- **Correct composition**
- **Sterility of the product**
- **Correct administration**

- Clinical checks
  - Chemotherapy regimen, patient profile, BSA, dose calculation, premeds, lab values
- Preparation checks
  - Check of the calculations
  - Assembly of raw materials, preparation, finished product, LABELS
- Validation
  - Product (Microbiological, physiochemical stability)
  - Cross contamination (Operator technique, containment devices)
  - Computer program

Correct composition?

- If possible use pre-authorized protocols
- Do not use abbreviations
- Check always with 2 persons
- Check on
  - clinical aspects
  - Technical aspects
  - Validate before you go live!

Administration

- Careful selection of devices
- Checking on correct patients
- Checking on correct route of administration (IR ↔ IV)
- Checking on extravasation (before and during)
Importance of sterility?

§ Endangered population
§ Due to therapy (chemo and/or radiotherapy), patients have a compromised immune system.
§ More needed than for TPN patients
§ No microbial effects on short term

Microbial growth in cytotoxics - Irene Kramer

<table>
<thead>
<tr>
<th>Microbial growth in cytotoxics – Kohi Hama</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Education – Training</th>
</tr>
</thead>
</table>

Facilities

§ Centralised
§ Separate room
§ Qualification of the room
  ~ type preparation
  ~ type of equipment

Ventilation Tools

- USP 797 / PIC’S norm
How we implemented this?

To meet the 2nd order in prevention (EU directive)

PhaSeal in practice

How to protect environment and employees against cytotoxic agents, the UZ Ghent experience; JOPP 2001; Vol 6:4

Urine test results

Closed devices any help for sterility?
Microbiological challenge of 4 transfer devices compared to needle

- Evaluation of microbiological resistance / safety
- In “Worst case” and “Realistic” contamination level
- Recommendations for daily practice

Letters in Applied Microbiology 47; 2008; 543-548

DETECTION METHOD = CHEMSCAN

- Solid Phase Cytometry
  - Quick (30 min incubation, results in 45 min)
  - Specific = Detection of fluorescent microorganisms by argon laser scanning
  - Precise: Counts from 1 micro organism to aborted scan (>30,000)

FLUORESCENCE ?

- Non-fluorescent substrate chemchrome v6 is taken up by metabolically active cells
- Substrate is cleaved by intracellular enzymes into green fluorescent carboxyfluorescein which can be retained in intact cells only.

DIFFERENCIATION M.O. ↔ PARTICLES ?

1. COLOR RATIO
   = Ratio height signal fluorescence in green light (500-530 nm) to orange light (540-585 nm)
2. SPECIFIC LIGHT INTENSITY
   = Ratio of signal amplitude to size
3. SHAPE OF SPECTRUM
   (1 → 3 = COMPUTERIZED)
4. VISUAL CONFIRMATION BY EPIFLUORESCENCE MICROSCOPE

CONTAMINATION OF VIAL DOP

- PSEUDOMONAS AERUGINOSA
  - 40 µL 10^4 OVERNIGHT CULTURE
    => 4 X 10^5 (= R.C.)
  - 40 µL 10^2 OVERNIGHT CULTURE
    => 4 X 10^6 (= W.C.)
**WORST CASE SCENARIO**

![Graph showing worst case scenario]

**ANOTHER WAY TO REPRESENT**

<table>
<thead>
<tr>
<th>Initial Contamination</th>
<th>PhaSeal</th>
<th>Chemo Spike</th>
<th>Clave valve</th>
<th>Securmix</th>
</tr>
</thead>
<tbody>
<tr>
<td>400,000</td>
<td>1/46</td>
<td>1/24</td>
<td>1/6</td>
<td>1/15</td>
</tr>
<tr>
<td>4000</td>
<td>1/40</td>
<td>1/24</td>
<td>1/7</td>
<td></td>
</tr>
</tbody>
</table>

Very good correlation between Worst case and Realistic

**CONTAMINATION OF TRANSFER DEVICE with Pseud.Aer.**

- 10 µL 10^5 O.N.C. (W.C.C.)
- 10 µL 10^4 O.N.C. (R.C.)

![Images of transfer devices]

**RESULTS MULTIPLE CONNECTIONS M.O. IN THE VIAL (N = 10) W.C.**

![Graph showing results]

**CONCLUSION CONCERNING MICROBIOTLOGICAL CHALLENGE**

- § PhaSeal® significant safer (> 1 to 2 log unit difference) compared to all other systems and needle in multiple handling!
- § The Critical Point is the “Dopping” Phase!
- § Need for validated decontamination process

**Decontamination + Damping protector**

<table>
<thead>
<tr>
<th>SPECIES</th>
<th>Contaminate with</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Staphylococcus Aureus</em></td>
<td>2 X 10^7</td>
</tr>
<tr>
<td><em>Pseudomonas Aeruginosa</em></td>
<td>4 X 10^7</td>
</tr>
<tr>
<td><em>Candida Albicans</em></td>
<td>1 X 10^8</td>
</tr>
<tr>
<td><em>Aspergillus Niger</em></td>
<td>2 X 10^9</td>
</tr>
</tbody>
</table>
**Key Questions !**

- **CHEMICAL / PHYSICAL STABILITY**
  - Literature, databases, ...
  - CRITICAL POINT = STERILITY
  - Validated procedure / devices
  - Keep vials longer

- If legally admitted, the Hospital Pharmacist is the only person who can take the responsibility for keeping punctured vials for longer period.

- He/she must take that decision based his/her local conditions and regulations

**Scenario 1**

- For **scenario 1** we used the drug vials available on the Belgian market and calculated for each preparation the optimum number of vials needed to prepare each dose individually.

- single preparation 187 mg
  - 1 vial of 100 mg + 1 of 50 mg + 4 of 10 mg

**Scenario 2**

- For **scenario 2** we calculated the number of different vials needed to prepare the prescribed dosages, **cumulated for one day**.

- 525 mg scheduled for that day
  - 5 vials of 100 mg + 3 of 10 mg

**Discussion : Conflict of interest by Pharmaceutical Companies**

- The recent years more and more research has been done on the chemical / physical stability of cytotoxic drugs after dissolving and in further dilution. Given the conflicting interest, this type of research is done by other parties (academic, hospital pharmacy, ...) then the pharmaceutical industry.

- Most of the time, the expiry time is limited to 24 hrs, arguing that the sterility cannot be guaranteed over a longer period.

**Scenario 1**

- For **scenario 1** we used the drug vials available on the Belgian market and calculated for each preparation the optimum number of vials needed to prepare each dose individually.

- single preparation 187 mg
  - 1 vial of 100 mg + 1 of 50 mg + 4 of 10 mg
Scenario 3

For **scenario 3** we calculated the number of vials needed, based on the highest volume and/or concentration available on the market and taking into account the maximum expiry date found in the literature.

**stability of cisplatinum = 14 days**

→ Only 100 mg vials are used

**Scenario 1**

= per preparation

: single preparation 187 mg

→ 1 vial of 100 mg + 1 of 50 mg + 4 of 10 mg

**Scenario 2**

= per day

: 525 mg scheduled for that day for 3 patients

→ 5 vials of 100 mg + 3 of 10 mg

**Scenario 3** = until end chemical stability or 14 days

→ Only 100 mg vials are used

Billing in all 3 scenarios is the same

Government pays based on vials as close as possible to what the patient received in therapy

---

**Number and products**

In total **3086** preparations are evaluated.

In the observation period, **39 different products** were used with a top 10 of most used products:

<table>
<thead>
<tr>
<th>Product</th>
<th>Number of Preparations</th>
</tr>
</thead>
<tbody>
<tr>
<td>FLUOROURACIL</td>
<td>718</td>
</tr>
<tr>
<td>CYCLOPHOSPHAMIDE</td>
<td>225</td>
</tr>
<tr>
<td>ETOPOSIDE</td>
<td>182</td>
</tr>
<tr>
<td>CISPLATINE</td>
<td>178</td>
</tr>
<tr>
<td>DOXORUBUCINE</td>
<td>177</td>
</tr>
<tr>
<td>CYTOMINTINE</td>
<td>150</td>
</tr>
<tr>
<td>DEMÉTICARINE</td>
<td>151</td>
</tr>
<tr>
<td>VINCristine</td>
<td>133</td>
</tr>
<tr>
<td>OXALIPLATINE</td>
<td>116</td>
</tr>
<tr>
<td>IRINOTECAN</td>
<td>103</td>
</tr>
</tbody>
</table>

---

**Results : Difference in drug costs over a period of 2 months**

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Financial Value (Euros) of Used Drug Vials</th>
<th>Difference in Euro Compared to Scenario 0</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scenario 1</td>
<td>839196</td>
<td>788179</td>
<td>73829</td>
</tr>
<tr>
<td>Scenario 2</td>
<td>73209</td>
<td>67217</td>
<td>6192</td>
</tr>
<tr>
<td>Scenario 3</td>
<td>73829</td>
<td>6192</td>
<td>6192</td>
</tr>
</tbody>
</table>

---

**Results : Number & cost of Protector**

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Number</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scenario 1</td>
<td>2172</td>
<td>6520</td>
</tr>
<tr>
<td>Scenario 2</td>
<td>205</td>
<td>1686</td>
</tr>
<tr>
<td>Scenario 3</td>
<td>211</td>
<td>1961</td>
</tr>
</tbody>
</table>

**Total**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Number</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>2172</td>
<td>6520</td>
</tr>
<tr>
<td>Stage 2</td>
<td>205</td>
<td>1686</td>
</tr>
<tr>
<td>Stage 3</td>
<td>211</td>
<td>1961</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>2198</td>
<td>6977</td>
</tr>
</tbody>
</table>
Results: Total cost difference

<table>
<thead>
<tr>
<th>Scenario 1</th>
<th>Scenario 2</th>
<th>Scenario 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product</td>
<td>8,875,678</td>
<td>7,825,678</td>
</tr>
<tr>
<td>Protectors</td>
<td>902,145</td>
<td>2,922,000</td>
</tr>
<tr>
<td>Total</td>
<td>9,777,823</td>
<td>9,747,678</td>
</tr>
</tbody>
</table>

Difference with scenario 3 (€): 33,400
Difference in % with scenario 3: +15.3% +7.0%

Discussion: % costs due to PhaSeal

§ Approx 50% of the costs = Protectors
§ Approx 50% of the costs = Injector + Connector

→ COST = 4.4% and 8.6% OF DRUG COST

What is the cost of safety?

Cost 4.4% to 8.6%
Staff is secured (CHEMICAL)
CTSD
Enhanced safety for Product (MO)
Savings (7% to 15%)

Other factors to consider!

✓ Negotiation with pharmaceutical/generic companies about “off patent” drugs (Up to > 50 – 60% discount)
✓ In some countries submitted for approval of reimbursement
✓ What is the cost of “in case off”...eg human harm, to appear in court, bad publicity,....

Implementation in general

1/ Start with simple easy to change things
2/ Centralize your preparations
3/ Use closed devices to ensure safety for the staff and the patient.
4/ Work on a better “clean environment”
5/ Validate your working procedures
6/ Use beyond the “magical” 24 Hours limit up to the last droplet according to the chemical-physical stability
7/ Safe money to invest further into safety and service.
Documented & electronic prescription and label

Centralised preparation in Pharmacy

Separated room with neg pressure

Personal protection (level 4)

BSC type 2 B 2 (level 3)

External exhaust
Closed system (level 2)

Cleaning & decontamination of vials

Dopping of the protector

Storage of dissolved product or restfractions

Preparation with PhaSeal

Preparation forms
Controlling the preparation

Near Future:
- Multispec laser resonance spectometry

Secure and seal before transport

Transport to the ward

C.A.S. infusion lines

Closed system of administration

DRY connection technique for intravenous administration of cytotoxics
ISOPP safety standard

✓ > 10,000 copies have already been distributed in 22 different countries around the world
✓ Audit tool is next project of ISOP standards committee
✓ Join ISSOP, the only world wide organisation of oncology pharmacists
✓ www.isopp.org

To end with …

IF YOU UNDERSTAND THE RISKS ….. YOU CAN COPE WITH THEM