

Contamination of external surface of cytotoxic vials:
what are the answers from manufacturers ?

October 8th 2009

Industrial Decontamination Process




Contamination of external surface of cytotoxic vials:
what are the answers from manufacturers ?

Decontamination – Necessity

- For operators loading filled product into transport trays
- For operators loading particulate inspection machines
- For operators following sampling procedures
- For operators performing chemical/ microbiological testing
- For operators on packaging lines
- For the end – user
- For the environment




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Decontamination – Manual or Automatic?

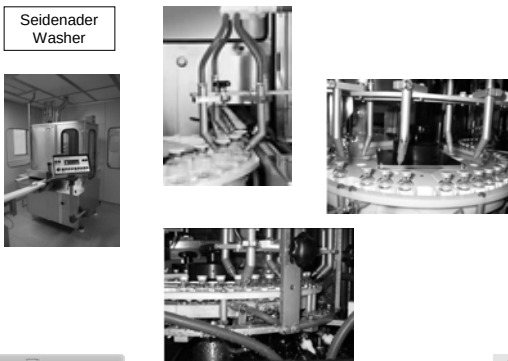
- **Manual cleaning NOT preferred**
 - Labour intensive and therefore costly
 - Some risk of operator exposure and also potential breakage
 - Reproducibility suspect – people get tired!
- **Automatic cleaning preferred**
 - Remote from operators; performed in closed environment
 - Reproducibility good and proven by validation
 - Collection and treatment of washing fluids before discharge
- **Cleaning fluids**
 - Purified water is preferred, followed by compressed air drying
 - Detergent residues could prevent application of labels




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Automatic Decontamination

Seidenader Washer





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Libra Washer



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Ultra Decontamination Washer, aut.



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Automatic Decontamination

- Washing patterns**
 - From the neck of the vial downwards, including the base.
 - For the Seidenader style of washer, water is sprayed at pressure through angled jets down around each vial and at the base. Product contamination removed by the water proceeds to the drain.
 - For the Libra style of washer, water is sprayed at pressure into the basket through jets and creates a spiral around each vial. Product contamination removed by the water is drawn toward the bottom of the basket and proceeds to the drain.
 - There is possibility of cytotoxic aerosol generated so this procedure is performed within containment
 - The isolator may be operating under negative pressure to protect the operators



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Automatic Decontamination

- Washing patterns**
 - The top of the rubber stopper is not washed after filling
 - Annexe 1 requirements for Grade A in all filling, stoppering and capping zones.
 - Therefore impossible to wash down a stoppered vial in a Grade A environment from both particulate and microbiological considerations; must rely upon accurate positioning of the filling needles to deliver the dose accurately into the vial
 - The top of any plastic cap is not washed after filling
 - There should be no free product at the capping stage
 - If water were sprayed onto the cap, it could collect under the plastic as there is a small gap between the bottom of the plastic and the top of the aluminium.
 - It would be very difficult to remove this water
 - If not effectively dried, moulds could grow on top on the rubber stopper, under the plastic cap



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Automatic Decontamination

- Washing fluid and drying air**
 - Normally ambient temperature but dependant upon drug stability
 - If the product can be heat sterilised then increased temperatures can be used at this stage
 - Important that fluid flows are consistent and any blocked needles are identifiable
 - Inconsistent flows would cause cleaning to be inconsistent and fail to meet validated criteria
- Disposal of washing residues**
 - Need to be treated with chemical agent to destroy cytotoxic materials before discharge to drain
 - Need to confirm that the results of this destruction are not themselves dangerous mutagens by applying Ames test
 - Agent selected, established in laboratory scale and industrialised
 - Validation of destruction process at industrial scale



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Automatic Decontamination

- Disposal of any residues from autoclaving**
 - If the product is terminally sterilised, there is a possibility of vials breaking in the autoclave chamber under extreme temperature/pressure conditions
 - Autoclave cycle needs to incorporate a final washing stage to ensure no cytotoxic residues.
 - All condensate and washing liquid needs to be treated with chemical agent to destroy cytotoxic materials before discharge to drain
 - Need to confirm that the results of this destruction are not themselves dangerous mutagens by applying Ames test
- Disposal of any contaminated solids (tubing, filters etc)**
 - Typically heated between 1100 and 1250 Celsius with excess oxygen to ensure all organics are totally destroyed.



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Validation of the Process

- Worst Case consideration**
 - Cover the outside of vials with the contained dose (to simulate breakage)
 - Possible to group products by solubility, pH of bulk solution etc
 - Allow to dry on if possible for "worst case" challenge
 - Replace on in-feed to washer and operate normally
 - Swab or rinse samples taken from vials after washer
 - Recovery studies on methodology



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What is an acceptable residue?

- Methods of Determination used in validation of decontamination process**
 - HPLC analysis on swabs or rinse sample is the preferred method as it can specifically target the cytotoxic agent
 - Total Organic Carbon analysis can be influenced by excipients
- Limits of Detection**
 - The limits of detection using HPLC methods are generally 10^1 to 10^2 µg/L and 10^{-1} to 10^0 µg per swab for rinse and swab samples respectively (Oxaliplatin, docetaxel, methotrexate, gemcitabine, irinotecan)
- Limits of Quantitation**
 - The limits of quantitation using HPLC method are generally 10^1 µg/L and 10^1 µg per swab for rinse and swab samples respectively (Oxaliplatin, docetaxel, methotrexate, gemcitabine, irinotecan)



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What is an acceptable residue?

Limits for potential cytotoxic contamination on exterior vial surfaces can be derived from the following general formula

$$\text{Limit} = \frac{\text{OEL}}{N \times K \times P} \mu\text{g /vial}$$

Where:

OEL = Occupational Exposure Limit, defined as acceptable continuous exposure 8rs/day, 5 days/week, for a 40 year working life (this is based upon an inhalation level, which must be considered worst case).

K = Absorption factor (proportion of contamination absorbed as a result of contact and taken to equal 0.1 unless there is specific evidence to the contrary)

N = Number of contacts per hour (taken to equal 5 unless there is specific evidence to the contrary)

P = Proportion of the vial in contact with the hand (taken to be 0.25), assuming trans-dermal absorption through/ no gloves



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What is an acceptable residue?

So e.g. for docetaxel (OEL is 1 µg per cubic metre air)

$$\text{Limit} = \frac{1}{5 \times 0.1 \times 0.25} \mu\text{g /vial} = 8 \mu\text{g /vial}$$

So e.g. for oxaliplatin (OEL is 0.7 µg per cubic metre air)

$$\text{Limit} = \frac{0.7}{5 \times 0.1 \times 0.25} \mu\text{g /vial} = 5.6 \mu\text{g /vial}$$


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Conclusion

- Industry takes every reasonable action to remove any external decontamination
- Acceptable residue amounts are being continuously reviewed downwards
 - As analytical techniques improve
 - As scientific data reveals previously unknown concerns
- Decontamination machines are continuously improved to increase washing efficacy
 - As more effective systems are devised
 - As more energy efficient systems are invented
- For the protection of the operators, technicians
- For the protection of the end-user

For the environment



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