Martina Kirwan
EPA Inspector
Licence Enforcement,
Office of Environmental Enforcement,
Environmental Protection Agency,
Seville Lodge, Callan Road,
Kilkenny.
Date: 22-May-2009

Abbott Ireland Limited IPPC Licence: P0847-01

Re: Request for Waste Stream Re-Classification

Dear Martina,

In accordance with Condition 1.4 of Abbott's IPPC Licence (P0847-01) Abbott would like to advise the agency that Abbott is seeking to makes classification changes to one of it's waste streams and requests prior agreement from the Agency to do so. The waste in question is 'DES Solid Waste'. Currently all wastes leaving our Drug Eluting Stent (DES) Manufacturing Suite are considered hazardous (EWC: 070513*). Abbott would like to split the waste coming from DES into two waste types:

1. '***Drug contaminated wastes':*** wastes that have been in direct contact with drug materials (eg, drug powder and/or drug in solution.) Types of wastes that fall into this category include drug pouches, drug contaminated wipes, contaminated gloves, drug coated stents, expired drug powder and/or drug solution, etc. These wastes will continue to be disposed of under the current 070513* classification.

2. '***DES general wastes'*** (eg, paper, plastic packaging, cardboard, etc.). These wastes are not hazardous as they have no hazardous constituents and have no direct contact with drug nor do they originate from manufacturing areas where drug powder is being weighed or mixed, eg, drug formulation rooms.

Abbott would like to advise the agency that following a comprehensive study of the background levels of drug contamination in it's DES manufacturing suites Abbott now is satisfied that 'DES General Waste' is not Hazardous and should be classified as: EWC 070514 – Solid Waste other than that mentioned in 070513*.

This request is supported by the completion of appropriate testing. Based on the levels of contamination identified in the attached study 'DES General Wastes' are not hazardous.

Kind Regards,

**Nigel Hickey**
Environmental Coordinator
EHS Department
Abbott Vascular
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Appendices: (1) Hazardous Waste Process Description (2) Hazardous Waste Classification Worksheet (3) Contamination Study.

## Appendix 1 - Hazardous Waste Process Background

**Waste Origin Description:**
Small quantities of drug powder (typically <20g) is weighed out 3 to 4 times a week in a dedicated powder weighing hood which is located in a separate room (Formulation Room) within the DES manufacturing suite. The powder once weighed is transferred to an adjacent fume cupboard where the powder is mixed with solvent to form the coating solution used to coat the cardiac stent. All waste removed from the formulation room is considered hazardous and is disposed of as such. This is a safety first approach to plan for any accidental contamination of general waste items (eg, paper) within the room. All operatives handing drug are trained on procedures to be taken to avoid accidental contamination.

Powder Hood

The coating solution is removed for the Formulation Room and transferred to the DES manufacturing area where it is then used within contained 'glovebox' systems to coat the stent.

Glovebox

Waste items removed for the inside of the glovebox (eg, cleaning wipes, scrap stents, etc.) are disposed of as hazardous waste. All other non chemical 'general wastes' produced within the manufacturing suite (eg, paper, plastic packaging, etc.) which are not in direct contact with drug are not deemed to be hazardous.

**Note:** The medical device industry uses only small quantities of drug in a cleanroom environment and would have similarities in scale with use of a hazardous powder within a laboratory fumehood. The items used directly within the fumehood and items of PPE like gloves would be considered hazardous but other general waste items produced within the lab (eg, paper, plastic, etc.) would not be considered hazardous.

The manufacturing process at Abbott Vascular does not use bulk quantities of drug and as consequence the likelihood of accidental contamination is remote. Where accidental contamination was to occur the levels of surface contamination would only be at trace levels in the low micrograms. This level does not pose any risk to persons and/or the environment.

The assessment methodology used for assessment of 'DES general waste' materials is as follows:

## 1. Waste Description:

The waste stream in question is made up of mixed general solid wastes (eg, paper, plastic wrapping, cardboard packaging, etc.) arising from the DES production facility at Abbott Vascular in Clonmel. These general wastes have no hazardous constituents and the risk of surface contamination by hazardous substances (drug) is considered very low, as verified by the attached study.

The facility manufactures cardiac stents that are coated with a potent compound called *'Everolimus'*. Everolimus is a hazardous substance and whilst this substance is handled by trained operatives in dedicated drug handling devices (ie, powder hoods and gloveboxes) there is a remote risk that general waste items may be accidentally contaminated with trace amounts of drug. Abbott had taken the prudent decision to classify all wastes leaving the DES area as Hazardous in the absence of a comprehensive contamination study to verify the actual levels of contamination in the manufacturing suite and on general waste items. This 'safety first approach' is inline with the policy followed by our sister manufacturing site in California.

*Abbott has now completed a full study of contamination levels in the DES area and based on the results of this study is seeking to re-classify 'DES General Waste Items' as being Non-Hazardous.*

| Waste Material | EWC Code | Main Source | Quantity | | On-site Recovery / Disposal | Off-0site Recovery, Reuse or Recycling | Off-Site Disposal |
|---|---|---|---|---|---|---|---|
| | | | Tonnes / month | M3 / month | (Method & Location) | (Method, Location & Undertaker) | (Method, Location & Undertaker) |
| Solid waste potentially contaminated with trace quantities of Drug (everolimus) | 070513* | D.E.S Production | 2.41 | - | N/A | N/A | Indaver Licence: Ref W0036-02 Final Destination: D10, AVG Germany, Licence: 107ZEB002 Indaver, Belgium: Licence: MLAVI/9800000485 |

## 2. Relevant EWC Listing

The waste stream in question (DES General Waste) has been classified up to this point as **070513* 'Solid Waste Containing Dangerous Substances'**. Abbott has previously considered this waste stream to be hazardous in the absence of definitive analytical evidence to prove otherwise.

## 3. Hazardous Substance Quantification

DES General Waste is not hazardous in nature unless accidentally contaminated by drug (Everolimus) above threshold limits. Accidental contamination although unlikely could occur with drug being picked up on gloves and transferred accidentally to other 'clean' areas and/or items.

There are strict documented procedures and formal training programs in place to avoid inadvertent contamination when drug or drug contaminated items are being handled.

In January 2009 Abbott completed a comprehensive surface contamination study of the manufacturing suite and 'general waste items' leaving it. (See section 6. Full results are also attached in Appendix 1.)

## 4. Hazardous Nature of Surface Contamination

Everolimus is an active pharmaceutical ingredient (API). The hazard classification of Toxic has been assigned to Everolimus: **R48** (Danger of serious damage to health by prolonged exposure.) and **R25** (Toxic if swallowed).

| Ref. Nº or | Material/ Substance(1) | CAS Number | Danger(2) Category | Amount Stored | Annual Usage | Nature of Use | R(3) - Phrase | S(3) - Phrase |
|---|---|---|---|---|---|---|---|---|
| 001 | Everolimus | 159351-69-6 | Toxic | 0.25kg | 1.5kg | DES Stent Drug Coat | R48/25 | S22, 45 |

## 5. Relevant Hazardous Waste Threshold limits

Based on the classification of Everolimus, DES solid waste could display the following hazardous properties:

| Classification | | | | Hazardous |
|---|---|---|---|---|
| Category of Danger | Risk Phrase | Substance Risk | Hazards | Waste Threshold Limit |
| Xn/T | R48 | Danger of serious damage to health by prolonged exposure. | H6 (H5) | **>= 3%** |
| T | R25 | Toxic if swallowed. | H6 (H5) | **>= 3%** |

## 6. DES Solid Waste Contamination Levels Summary

110 swab samples were taken to measure actual levels of contamination on fixed equipment and surfaces (eg, tables, walls, floors, etc.) within the DES manufacturing suite and general waste items removed form the area. A summary of the results are as follows:

- 98.2% of swabbed items (108 samples) showed zero drug contamination.
- 1.8% of samples (2 samples) showed minute trace levels of drug but at levels that were less than 1/5$^{th}$ of the acceptable occupational surface limit (occupational limit: 100mcg/100cm2) for Everolimus. Levels were found to be 10 and 17mcg/100cm2. (See detailed report Appendix 1.)

6 air samples were also taken and no drug was identified., ie, levels were below the level of detection for the analytical method, ie, <2.3mcg/m3.

In summary, little or no contamination is present within the suite. The items that showed trace levels of contamination were on fixed equipment, not waste items. And none of the 19 waste items that were sampled for drug contamination showed any drug whatsoever.

## 7. References


1. European Waste Catalogue and Hazardous Waste List, 2002, Environmental Protection Agency.
2. Hazardous Waste Classification Worksheet (Aug 2004).

# Appendix 3 – Everolimus Surface Swab Analysis Results

## GEHS - EUROPEAN REGIONAL SUPPORT

| | | | |
|---|---|---|---|
| REF | AV Clonmel Everolimus January 2009 | | |
| DATE OF ISSUE | **9th March 2009** | ISSUE Nº | **1** |
| AUTHOR | **Jon Peers** | PROJECT Nº | **1141** |

TITLE: AV CLONMEL: ASSESSMENT OF THE AIRBORNE & SURFACE SAMPLE CONCENTRATION OF EVEROLIMUS IN DES SUITE 1 & 2.


EXECUTIVE SUMMARY: Surface wipe samples for Everolimus were undertaken in the following areas to ascertain the potential for drug present on surfaces of the room and articles that leave the room currently labelled as '*hazardous waste'*.

- DES Suite 2,
- Formulation laboratory,
- QA Write-up Area
- Waste Storage Area
- Waste Handling Area

110 Surface swabs samples were taken with 98.2% of samples showing no detectable levels of Everolimus contamination.

Only 1.8% of samples (2 samples) showed detectable levels of Everolimus. These two samples showed Everolimus contamination levels which were below the Occupational Dermal Limit of 100mcg/100cm2, ie, 12 and 17 mcg/100cm2. The samples were located at the keyboard of the PC at Isolator 40 on Line 5 and the "glass" of isolator 53 on Line 4.1.

Based on the surface results obtained the risk of dermal exposure to employees may be considered as minimal, similarly the risk of general items leaving the suite with significant levels of surface contamination can be considered extremely remote.

6 air samples were taken with results below the level of detection (<2.3mcg/m3).


| DISTRIBUTION: | | |
|---|---|---|
| Nigel Hickey | Environmental Coordinator | |
| Annabelle Donovan | EHS Group Lead | |
| Michael Ryan | Facilities/EHS Manager | |
| Steven Moylan | Abbott Global EHS Support. | |

## 1.0 OBJECTIVE

Surface wipe samples for Everolimus were undertaken in the following areas to ascertain the potential for drug contamination on surfaces of the room and 'general waste articles' that leave the room currently labelled as 'hazardous waste'. The data presented in this report represents conditions existing at these locations on the days of these studies. The areas targeted were areas where the risk of surface contamination would be considered greatest. The areas targeted were:

- DES Suite 2,
- Formulation laboratory,
- QA Write-up Area
- Waste Storage Area
- Waste Handling Area

## 1.1 OCCUPATIONAL EXPOSURE LIMIT

The Abbott EEL is a health-based limit, derived solely from health-related data. It is expressed as an average concentration of a substance present in the breathing zone of a person over a specified reference period. The EEL's value is such that there is no evidence, according to current knowledge, that the substance is likely to have any effect on the health of employees if they are exposed by inhalation, day after day, to that concentration.

### 1.1.2. Everolimus EEL/OEL – 5mcg/$m^3$

### 1.1.3 Occupational Dermal Limit

$$\text{Occupational Dermal Limit (CL) (mcg/100 cm2)} = \frac{\text{EEL (mcg/m3) x air breathed (m3)}}{\text{skin absorption factor [100 cm2 sampled]}}$$

Assumptions:

- use appropriate EEL (5mcg/m3)
-skin absorption factor (Use 50% (0.5) unless for the API the exact dermal absorption rate is known) typically very conservative
-10 m3 air breathed/8 hr workday
-area of exposed skin is assumed to 100 cm2

Occupational Dermal Limit = **100 mcg/100cm2.**

## 1.2 METHODOLOGY

See Appendix A

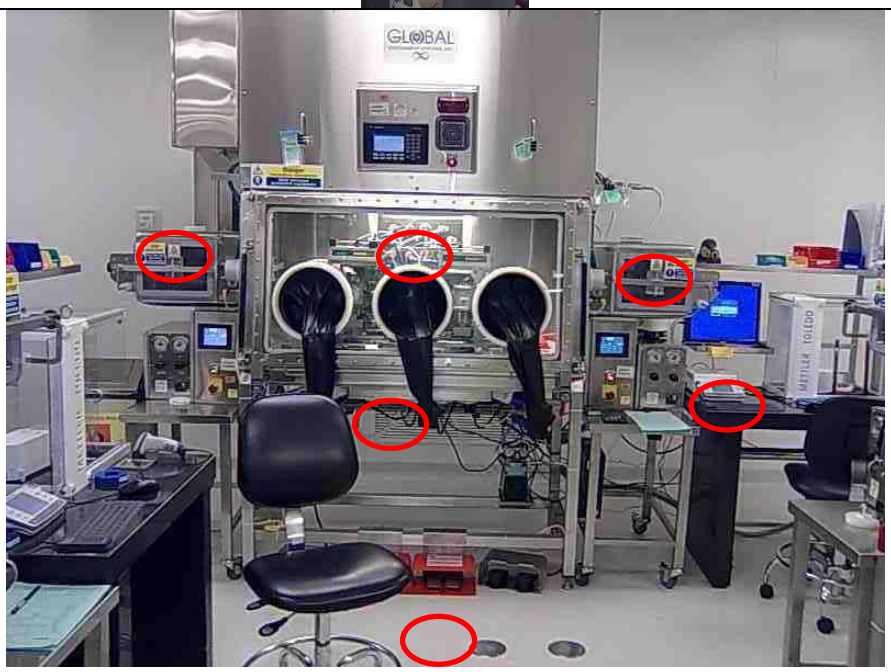
- Air Samples were taken using Abbott GEHS Laboratory method 6115.
- Surface Samples were taken using Abbott GEHS Laboratory method 6126.

## 2.0 RESULTS/DISCUSSION

Surface Swab Samples Summary Table:

| DES LINE 2 | Line 6.2 | | Line 6.1 | | Line 5 | | Line 4.1 | |
|---|---|---|---|---|---|---|---|---|
| | 27th January | | 27th January | | 27th January | | 28th January | |
| Location | Ref | Result mcg/100cm2 | Ref | Result mcg/100cm2 | Ref | Result mcg/100cm2 | Ref | Result mcg/100cm2 |
| End of line | 7497 | <10 | 7515 | <10 | 7512 | <10 | 7581 | <10 |
| PC Workstation table | 7525 | <10 | 7550 | <10 | 7573 | <10 | 7584 | <10 |
| Automatic Stamp | 7438 | <10 | 7594 | <10 | 7508 | <10 | 7480 | <10 |
| Balloon Fold station | 7583 | <10 | 7489 | <10 | 7595 | <10 | 7473 | <10 |
| Top of horizontal air flow oven | 7490 | <10 | 7592 | <10 | 7459 | <10 | 7502 | <10 |
| | Isolator 42 | | Isolator 44 | | Isolator 46 | | Isolator 53 | |
| LHS Hatch of Isolator | 7456 | <10 | 7590 | <10 | 7513 | <10 | 7479 | <10 |
| Glass above glove port | 7561 | <10 | 7523 | <10 | 7593 | <10 | 7526 | 12 |
| RHS Hatch of isolator | 7505 | <10 | 7510 | <10 | 7532 | <10 | 7571 | <10 |
| Keyboard RHS Workstation | 7466 | <10 | 7551 | <10 | 7569 | <10 | 7474 | <10 |
| | Isolator 48 | | Isolator 41 | | Isolator 40 | | Isolator 54 | |
| LHS Hatch of Isolator | 7456 | <10 | 7535 | <10 | 7554 | <10 | 7475 | <10 |
| Glass above glove port | 7561 | <10 | 7553 | <10 | 7496 | <10 | 7478 | <10 |
| RHS Hatch of isolator | 7505 | <10 | 7509 | <10 | 7555 | <10 | 7507 | <10 |
| Keyboard RHS Workstation | 7504 | <10 | 7547 | <10 | 7533 | 17 | 7527 | <10 |
| | Isolator 45 | | Isolator 52 | | Isolator 43 | | Isolator 50 | |
| LHS Hatch of Isolator | 7476 | <10 | 7568 | <10 | 7514 | <10 | 7575 | <10 |
| Glass above glove port | 7501 | <10 | 7589 | <10 | 7511 | <10 | 7585 | <10 |
| RHS Hatch of isolator | 7545 | <10 | 7572 | <10 | 7516 | <10 | 7591 | <10 |
| Keyboard RHS Workstation | 7477 | <10 | 7588 | <10 | 7530 | <10 | 7494 | <10 |
| | | | | | | | | |
| Floor between 3 isolators | 7521 | <10 | 7576 | <10 | 7574 | <10 | 7500 | <10 |
| Air Exhaust Grill behind isolator | 7439 | <10 | 7586 | <10 | 7534 | <10 | 7549 | <10 |

## Sampling at manufacturing lines in DES Suite

| Swab Nº | Location | Photo |
|---|---|---|
| 1 | End of line |  |
| 2 | PC Workstation table |  |
| 3 | Automatic stamp afm |  |
| 4 | Balloon Hold station |  |
| 5 | Top of horizontal air flow oven |  |
| 6 | LHS Hatch of Isolator |  |
| 7 | Glass above glove port | |
| 8 | RHS Hatch of isolator | |
| 9 | Keyboard RHS Workstation | |
| 10 | LHS Hatch of Isolator | |
| 11 | Glass above glove port | |
| 12 | RHS Hatch of isolator | |
| 13 | Keyboard RHS Workstation | |
| 14 | Floor between 3 isolators | |
| 15 | LHS Hatch of Isolator | |
| 16 | Glass above glove port | |
| 17 | RHS Hatch of isolator | |
| 18 | Keyboard RHS Workstation | |
| 19 | Air Exhaust Grill behind isolator | |

Positions were repeated for each isolator.

**DES Drug Formulation Room**

| Sample Number | Location | Photo | Result mcg/100cm2 |
|---|---|---|---|
| **Formulation Room** – (Everolimus weighed out and mixed in this room.) | | | |
| 7446 | Top of Flow Science Powder Weigh Hood |  | <10 |
| 7458 | Base of Fumehood |  | <10 |
| 7488 | Top of Flammable cabinet |  | <10 |
| 7506 | Surface on granite weighstation |  | <10 |
| 7437 | Surface between keyboards | N/A | <10 |

| DES Drug Formulation Room, contd. | | | |
|---|---|---|---|
| **Sample Number** | **Location** | **Photo** | **Result mcg/100cm2** |
| 7481 | Door Exit Button |  | <10 |
| 7563 | Surface of Hepa Extract Filter |  | <10 |
| 7467 | RHS exit door handle |  | <10 |
| 7546 | Room air extraction grill |  | <10 |

| DES QA Write-up Area – Admin area only, no drug handling. | | | |
|---|---|---|---|
| 7566 | Table Surface |  | <10 |

| DES QA Write-up Area, contd. – Admin area only, no drug handling. | | | |
|---|---|---|---|
| **Sample Number** | **Location** | **Photo** | **Result mcg/100cm2** |
| 7482 | Table Surface |  | <10 |
| 7543 | Keyboard (Terminal 702465) |  | <10 |

**28th January**

| Sample Ref | Location | Result |
|---|---|---|
| DES SUITE 2 | | |
| 7471 | Gloves (Jon Peers) | <10 |
| 7495 | Gloves (Operator Line 4 Iso. 53) | <10 |
| 7472 | Waste Bin LHS of Iso. 50 Line 4 | <10 |
| 7565 | Waste Catheter Bin Line 4 (Inside) | <10 |
| 7422 | Drug Waste Bin 4.2 Lid | <10 |
| 7493 | Gloves (Operator Line 4.2 Iso 47) | <10 |
| 7582 | Drug Waste Bin Line 5 Lid | <10 |
| 7498 | Drug Waste Bine Line 5 inside | <10 |
| 7492 | Gloves (Operator Line 5 Iso 43) | <10 |
| 7556 | Drug Waste Bin Line 6.2 Inside | <10 |
| DES SUITE 2 Waste Room | | |
| 7552 | Floor | <10 |
| 7544 | Door Handle to exit to corridor | <10 |
| Waste Handling Area | | |
| 7499 | H2O Bottle (Waste bag 1) | <10 |
| 7548 | H2O Bottle (Waste bag 2) | <10 |
| 7483 | H2O Bottle (Waste bag 3) | <10 |
| 7491 | Catheter Shield (Waste bag 1) | <10 |
| 7567 | Catheter Shield (Waste bag 2) | <10 |
| 7570 | Catheter Shield (Waste bag 3) | <10 |
| 7484 | Gloves (Waste Bag 1) | <10 |
| 7470 | Gloves (Waste Bag 2) | <10 |
| 7524 | Gloves (Waste Bag 3) | <10 |

***Air Samples - Stent Spraying DES Suite 1***

Six area air samples were also taken over two days during the coating of stents with an Everolimus solution in Suite 1. The spray coating of stents is undertaken within isolators where coated and uncoated stents are passed through interlocked transfer ports on each side of each isolator.

| Date | Time | Location | Result | Photo |
|---|---|---|---|---|
| 27th Jan 09 | 90 mins | LHS Port of Isolator 69 Line 1.2 | <2.4 |  |
| | | Back of Isolator unit 73 Line 1.3 facing Line 1.2 | <2.3 |  |
| | | LHS Port of Isolator 71 Line 1.1 | <2.3 |  |
| 28th Jan 09 | 90 mins | LHS Port of Isolator 69 Line 1.2 | <2.3 |  |
| | | LHS Port of Isolator 68 Line 1.1 | <2.3 | |
| | | LHS Port of Isolator 67 Line 1.2 | <2.3 | |

All results were below the analytical limit of detection for Everolimus, ie, 2.3mcg/m3.

**3.0 RESULTS SUMMARY & CONCLUSION**

**3.1** 6 airborne samples detected no drug, ie, levels were below the analytical limit of detection (<2.3mcg/m3). These readings are consistent with previous samples taken within DES manufacturing.

*- Consequently the risk of airborne contamination of items within the DES Manufacturing Suite can be considered minimal.*

**3.2** 110 Surface swab samples were taken and 108 showed zero drug contamination. 2 samples showed presence of drug, but only at trace levels. The two samples in question were located on fixed equipment. The samples were located at:

- DES 2 at the keyboard of the PC at Isolator 40 on Line 5 (17 mcg/m3)
- DES 2 "glass" of isolator 53 on Line 4.1 (12 mcg/m3).

The levels of drug (Everolimus) detected were at trace levels only, ie, at 1/5$^{th}$ of the Occupational Dermal Limit of 100mcg/100cm2.

*- Based on the surface swab results obtained the risk of surface contamination of wastes may be considered as minimal. In the exception where contamination is picked up it is likely to be only at insignificant (trace) levels.*

(Note: 1mcg = 0.000001g)

**4.0 RECOMMENDATIONS**

1. Employees to continue to wear current PPE/RPE and use current controls.
2. The results must be communicated to all employees and similar exposure groups.
3. AV Clonmel to compare the above levels with threshold limits used for defining wastes as hazardous.
4. Where agreement is received from the EPA to re-classify general wastes as non hazardous, perioidic re-swabbing should be completed to verify that the levels of contamination within DES remain insignificant.

**Jon Peers**
Occupational Hygiene & Safety Specialist

GEHS Regional Support

# APPENDIX A

## Air Sampling Lab Method 6115

Method Information

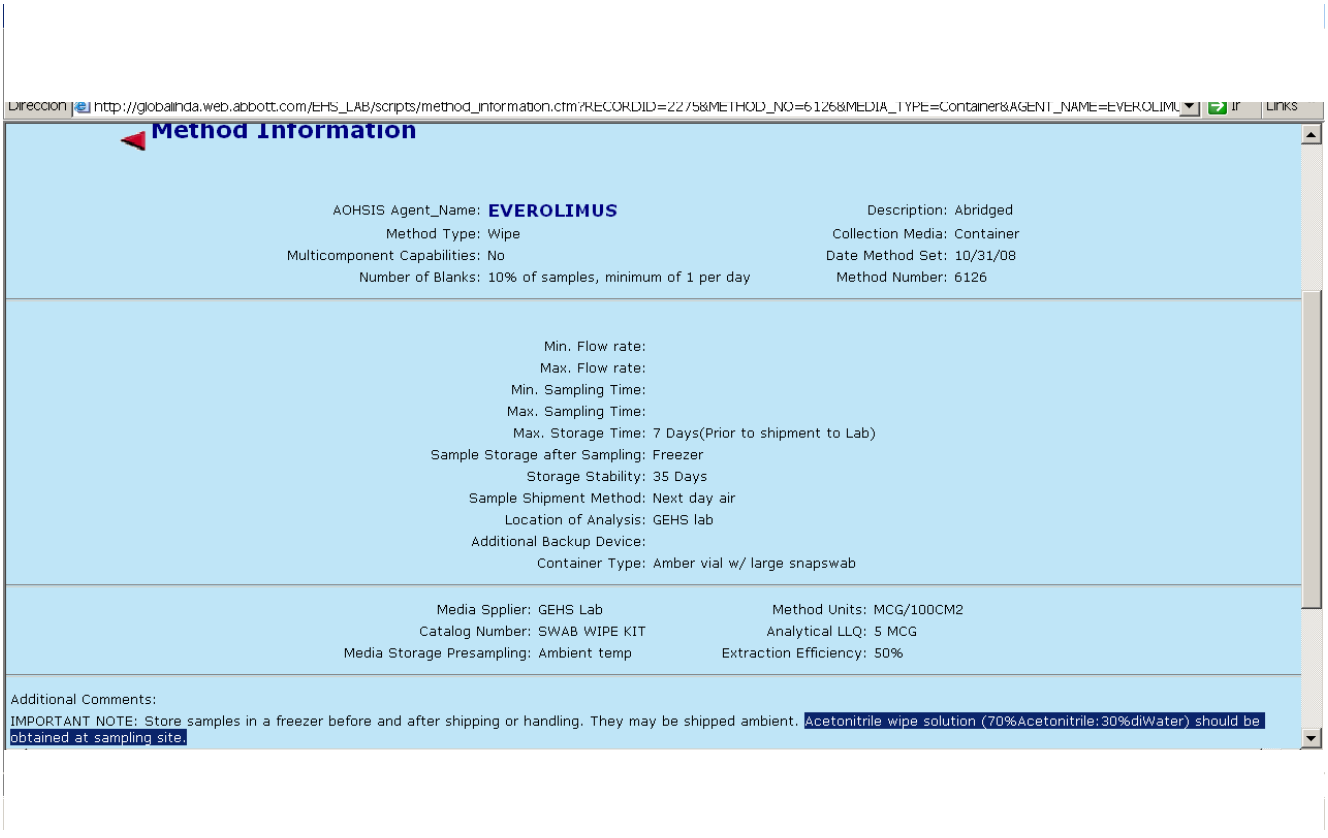
AOHSIS Agent_Name: EVEROLIMUS
Method Type: Air
Multicomponent Capabilities: No
Number of Blanks: 10% of samples, minimum of 1 per day
Description:
Collection Media: Filter
Date Method Set: 06/17/08
Method Number: 6115

Min. Flow rate: 2000 mL/min
Max. Flow rate: 2000 mL/min
Min. Volume: 150 L
Max. Volume: 240 L
Max. Storage Time: 5 Days(Prior to shipment to Lab)
Sample Storage after Sampling: Freezer
Storage Stability: 28 Days
Sample Shipment Method: Next day air: ice packs
Location of Analysis: GEHS lab
Additional Backup Device:
Cassette Tape Color: Blue
Cassette Type: Polypropylene
Cassette Size: 25 mm
Cyclone Needed:
Filter Type: TEF (Teflon)
Filter Preweigh:
Filter Pore Size: 1 um
Backup Pad Type: Polypropylene
Pretreatment:

Media Spplier: GEHS Lab
Catalog Number: 25MM BLUE/BLACK
Media Storage Presampling: Ambient temp
Method Units: MCG/M3
Analytical LLQ: 0.36 MCG
Extraction Efficiency: 64%

Additional Comments:
NOTE max sampling time of 120 minutes or 240 LTR. For longer sampling times, collect multiple cassettes. An air volume of 150 LTR (75 minutes) is necessary to detect at the AL of 2.5 mcg/m3. Samples must be stored frozen;can ship refrigerated.

## Wipe Sampling Method 6126



Direccion http://globalinda.web.abbott.com/EHS_LAB/scripts/method_information.cfm?RECORDID=2275&METHOD_NO=6126&MEDIA_TYPE=Container&AGENT_NAME=EVEROLIMU

Method Information

AOHSIS Agent_Name: EVEROLIMUS
Method Type: Wipe
Multicomponent Capabilities: No
Number of Blanks: 10% of samples, minimum of 1 per day
Description: Abridged
Collection Media: Container
Date Method Set: 10/31/08
Method Number: 6126

Min. Flow rate:
Max. Flow rate:
Min. Sampling Time:
Max. Sampling Time:
Max. Storage Time: 7 Days(Prior to shipment to Lab)
Sample Storage after Sampling: Freezer
Storage Stability: 35 Days
Sample Shipment Method: Next day air
Location of Analysis: GEHS lab
Additional Backup Device:
Container Type: Amber vial w/ large snapswab

Media Spplier: GEHS Lab
Catalog Number: SWAB WIPE KIT
Media Storage Presampling: Ambient temp
Method Units: MCG/100CM2
Analytical LLQ: 5 MCG
Extraction Efficiency: 50%

Additional Comments:
IMPORTANT NOTE: Store samples in a freezer before and after shipping or handling. They may be shipped ambient. Acetonitrile wipe solution (70%Acetonitrile:30%diWater) should be obtained at sampling site.