Preventing of Cross Contamination

ISPE – PDA Conference Australia
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20th September 2019

Richard Denk
Senior Consultant Aseptic Processing & Containment
SKAN AG
Richard.denk@skan.ch

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Agenda

1	**Cleaning Validation**
2	**Occupational Hygiene Validation**
3	**Question and Answer**

3 Key Factors for Aseptic Toxic Processing

Cleaning/Cross Contamination	H_2O_2 Decontamination	Operator Protection
▪ Requirements get higher in aseptic processing ▪ Validation of Cleaning and Disinfection ▪ New to the BioTech	▪ Process well established ▪ Isolator Technology ▪ Vaporized Hydrogen Peroxid vH_2O_2	▪ Requirements for high potent substances ▪ Less Experience with aseptic Isolators
		

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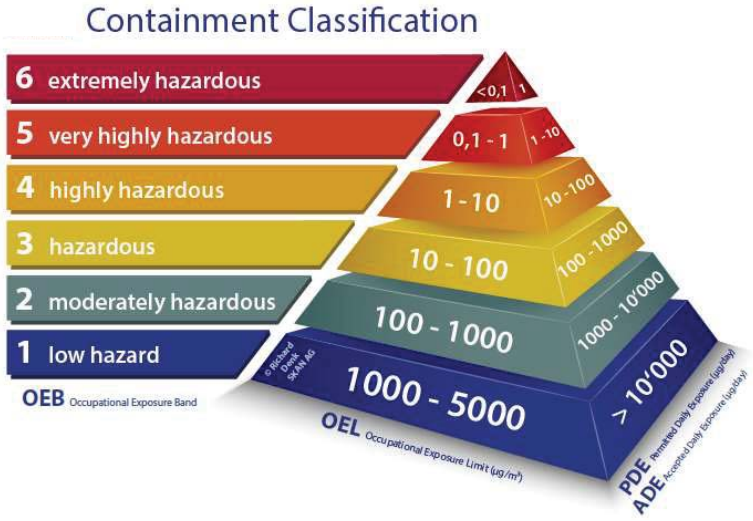
Why Cleaning in Aseptic Isolators

Requirements on cGMP and Work Hygienic Validation



Key Reason for Update of the Annex 1

Annex 1 update

Key reasons for update

- Contamination control strategy
  - Linked to 3.6, 5.20, 5.21
  - Understand facility
  - Understand Equipment
  - Understand process
  - Update based on feedback

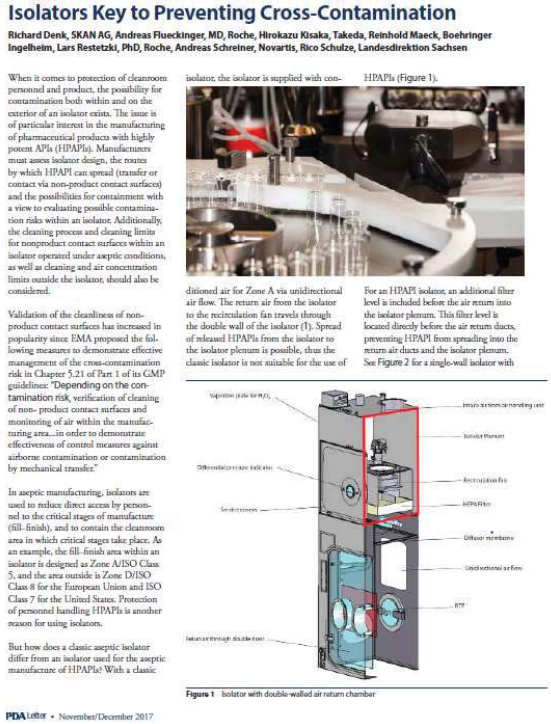
Andrew Hopkins
Introduced during the Annex 1 Workshop in Washington DC on the 2nd and 3rd of October

MHRA
Regulating Medicines and Medical Devices

Chapter 5.20:
New Requirements Based on the EMA Guideline on Setting Health-Based Exposure Limits in shared facilities based on the PDE „Permitted Daily Exposure“

Chapter 5.21:
“Depending on the contamination risk, verification of cleaning of non- product contact surfaces and monitoring of air within the manufacturing area [...] in order to demonstrate effectiveness of control measures against airborne contamination or contamination by mechanical transfer.”

Cleaning Method



Isolators Key to Preventing Cross-Contamination

Richard Denk, SKAN AG, Andreas Flueckinger, MD, Roche, Hirokazu Kisaka, Takeda, Reinhold Maeck, Boehringer Ingelheim, Lars Restetzki, PhD, Roche, Andreas Schreiner, Novartis, Rico Schulze, Landesdirektion Sachsen

When it comes to protection of cleanroom personnel and product, the possibility for contamination both within and on the exterior of an isolator exists. The issue is of particular interest in the manufacturing of pharmaceutical products with highly potent APIs (HPAPIs). Manufacturers must assess isolator design, the routes by which HPAPI can spread (transfer or contact via non-product contact surfaces) and the possibilities for containment with a view to evaluating possible contamination risks within an isolator. Additionally, the cleaning process and cleaning limits for nonproduct contact surfaces within an isolator operated under aseptic conditions, as well as cleaning and air concentration limits outside the isolator, should also be considered.

Validation of the cleanliness of non-product contact surfaces has increased in popularity since EMA proposed the following measures to demonstrate effective management of the cross-contamination risk in Chapter 5.21 of Part 1 of its GMP guidelines: "Depending on the contamination risk, verification of cleaning of non- product contact surfaces and monitoring of air within the manufacturing area...in order to demonstrate effectiveness of control measures against airborne contamination or contamination by mechanical transfer."

In aseptic manufacturing, isolators are used to reduce direct access by personnel to the critical stages of manufacture (fill–finish), and to contain the cleanroom area in which critical stages take place. As an example, the fill–finish area within an isolator is designed as Zone A/ISO Class 5, and the area outside is Zone D/ISO Class 8 for the European Union and ISO Class 7 for the United States. Protection of personnel handling HPAPIs is another reason for using isolators.

But how does a classic aseptic isolator differ from an isolator used for the aseptic manufacture of HPAPIs? With a classic isolator, the isolator is supplied with conditioned air for Zone A via unidirectional air flow. The return air from the isolator to the recirculation fan travels through the double wall of the isolator (1). Spread of released HPAPIs from the isolator to the isolator plenum is possible, thus the classic isolator is not suitable for the use of HPAPIs (Figure 1).

For an HPAPI isolator, an additional filter level is included before the air return into the isolator plenum. This filter level is located directly before the air return ducts, preventing HPAPI from spreading into the return air ducts and the isolator plenum. See Figure 2 for a single-wall isolator with

Figure 1 Isolator with double-walled air return chamber

PDA Letter • November/December 2017

Validation of the cleanliness of non-product-contact surfaces has increased in popularity since the EMA proposed the following measures in order to demonstrate effective management of the cross-contamination risk (in Chapter 5.21 of Part 1 of its GMP guidelines): “Depending on the contamination risk, verification of cleaning of non- product contact surfaces and monitoring of air within the manufacturing area [...] in order to demonstrate effectiveness of control measures against airborne contamination or contamination by mechanical transfer.”

What are the GMP and Occupational Safety Requirements

People • Science • Regulation

PDA Letter

www.pda.org/pdaletter November 6, 2017

Isolator Surfaces and Contamination Risks to Personnel and Patient

Richard Denk, SKAN AG, Andreas Flueckinger, MD, Roche, Hirokazu Kisaka, Takeda, Reinhold Maeck, PhD, Boehringer Ingelheim, Lars Restetzki, PhD, Roche, Andreas Schreiner, PhD, Novartis, Rico Schulze, Landesdirektion Sachsen

GMP Cleaning Requirements for Nonproduct Contact Surfaces

When it comes to protection of cleanroom personnel and product, the possibility for contamination both within and outside an isolator exists.

The issue is of particular interest in the fill–finish area within an isolator is designed as Zone A/ISO Class 5, and the area outside is Zone D/ISO Class 8 for the European Union and ISO Class 7 for the United States. Protection of personnel handling HPAPIs is another reason for using isolators.

But how does a classic aseptic isolator differ Spread of released HPAPIs from the isolator to the isolator plenum is possible; therefore, the classic isolator is not suitable for use of HPAPIs (**Figure 1**).

An HPAPI isolator, on the other hand, features an additional filter level before the air return into the isolator plenum. This filter

Cleaning Requirements based on limits in relation to the ADE/PDE combined with a risk identification and toxicology requirements

Risk Identification

The following scenarios of product spread in the isolator are possible:

1. **Spread due to turbulence caused by air flow (pressure cascades) within the isolator line.**
2. **Spread due to contaminated gloves.**
3. **Spread due to mechanical transfer systems such as conveyors, carousels, transport carriages for moving equipment to other sections of the isolator.**
4. **Contact contamination due, for example, to damaged vials and gloves, or contaminated stainless steel or plastic surfaces.**
5. **Spread due to transfer of contaminated settle plates (viable sampler)**

Air flow:

The spread of airborne particles or aerosols can be determined in advance during the planning stage by means of simulations. These simulations help when it comes to positioning the filters before the air return ducts, and in designing the air flow to the filters.

Risk Identification

Mechanical transfer:

During the aseptic fill-and-finish process, vials, syringes, etc. are transferred using conveyors, separating systems, lifting and transfer systems. These transfer systems can also result in the carry-over of highly active substances into neighbouring areas. This carry-over is critical in the following situations:
Open filling of vials, syringes, etc. The filling process leads to the release of aerosols that, over a shorter or longer period of time, can build up on, dry out and then be released from surfaces / transfer systems / filling equipment such as filling needles.
Breakage of vials. Vial breakage can occur at any time during the manufacturing process and result in contamination of mechanical transfer systems. Particularly critical points include the separation of the vials, the transfer of the vials via carousels, the loading and unloading of the freeze-dryer und finally the crimping of the vials.

Cleaning Method

Table 1 Proposed EH&S and GMP surface limits for non-product contact surfaces and air limits inside of isolators

Occupational Exposure Bands (OEBs) Acceptable worker exposure (µg/m³) *(8-hour time-weighted average). The acceptable exposure is the conservative end of the OEB.*	**Limit for surface with no direct product contact inside the isolator (µg/dm²)** *Acceptable based on GMP and occupational health criteria.*	**Limit for "public" surface with uncontrolled possibility of unprotected hand contact (µg/dm²)** *Driven by occupational health criteria only.*	**Limit for airborne API inside of isolator after cleaning at product changeover (µg/m³)** *Driven by GMP criteria only. ***
OEB 1: range 1000-5000 ug/m³ Exposure limit: 1000 ug/m³	Visually clean	Visually clean	10000
OEB 2: range 100-1000 ug/m³ Exposure limit: 100 ug/m³	Visually clean	100	1000
OEB 3: range 10-100 ug/m³ Exposure limit: 10 ug/m³	100	10	100
OEB 4: range 1-10 ug/m³ Exposure limit: 1 ug/m³	10	1	10
OEB 5: range 0.1-1 ug/m³ Exposure limit: 0.1 ug/m³	1	0.1	1
OEB 6: range less than 01 ug/m³ Exposure limit: 0.01 ug/m³ or lower	0.1 or lower	0.01 or lower	0.1 or lower

** This limit is safe under the assumption that as a maximum, the total API burden of the previous product suspended in 1 m³ of air inside the isolator would go into one single therapeutic dose of the following products. Please also consider above that for simplification reasons the PDE/OEL ratio of 10 was assumed in regard to cross-contamination. Be aware that this needs to be justified for each product and product sequence due to difference in adjustment factors and administration route.

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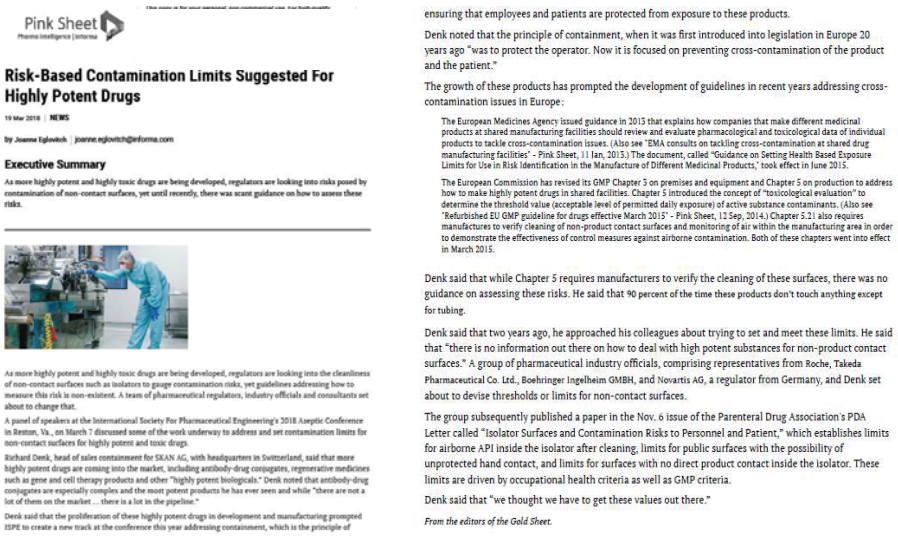
Cleaning Method

Steps of the Cleaning Method of non- product contact surfaces within aseptic Isolators:

- Risk identification based on the layout, Air Flow Simulation, routine operations within the isolator with gloves, Riboflavin Study.

- Cleaning requirements based on the ADE/PDE
  - Manual Cleaning
  - Semi automated cleaning
  - Fully automated cleaning
- Cleaning Method to demonstrate the effectiveness of the cleaning.
- Cleaning from less critical areas towards critical areas.
- Route of waste material

Additional Publications



Pink Sheet
Pharma Intelligence | informa

Risk-Based Contamination Limits Suggested For Highly Potent Drugs

19 Mar 2018 | NEWS

by Joanne Eglovitch | joanne.eglovitch@informa.com

Executive Summary

As more highly potent and highly toxic drugs are being developed, regulators are looking into risks posed by contamination of non-contact surfaces, yet until recently, there was scant guidance on how to assess these risks.

As more highly potent and highly toxic drugs are being developed, regulators are looking into the cleanliness of non-contact surfaces such as isolators to gauge contamination risks, yet guidelines addressing how to measure this risk is non-existent. A team of pharmaceutical regulators, industry officials and consultants set about to change that.

A panel of speakers at the International Society For Pharmaceutical Engineering's 2018 Aseptic Conference in Reston, Va., on March 7 discussed some of the work underway to address and set contamination limits for non-contact surfaces for highly potent and toxic drugs.

Richard Denk, head of sales containment for SKAN AG, with headquarters in Switzerland, said that more highly potent drugs are coming into the market, including antibody-drug conjugates, regenerative medicines such as gene and cell therapy products and other "highly potent biologicals." Denk noted that antibody-drug conjugates are especially complex and the most potent products he has ever seen and while "there are not a lot of them on the market ... there is a lot in the pipeline."

Denk said that the proliferation of these highly potent drugs in development and manufacturing prompted ISPE to create a new track at the conference this year addressing containment, which is the principle of ensuring that employees and patients are protected from exposure to these products.

Denk noted that the principle of containment, when it was first introduced into legislation in Europe 20 years ago "was to protect the operator. Now it is focused on preventing cross-contamination of the product and the patient."

The growth of these products has prompted the development of guidelines in recent years addressing cross-contamination issues in Europe:

> The European Medicines Agency issued guidance in 2013 that explains how companies that make different medicinal products at shared manufacturing facilities should review and evaluate pharmacological and toxicological data of individual products to tackle cross-contamination issues. (Also see "EMA consults on tackling cross-contamination at shared drug manufacturing facilities" - Pink Sheet, 11 Jan, 2013.) The document, called "Guidance on Setting Health Based Exposure Limits for Use in Risk Identification in the Manufacture of Different Medicinal Products," took effect in June 2015.
>
> The European Commission has revised its GMP Chapter 3 on premises and equipment and Chapter 5 on production to address how to make highly potent drugs in shared facilities. Chapter 5 introduced the concept of "toxicological evaluation" to determine the threshold value (acceptable level of permitted daily exposure) of active substance contaminants. (Also see "Refurbished EU GMP guideline for drugs effective March 2015" - Pink Sheet, 12 Sep, 2014.) Chapter 5.21 also requires manufactures to verify cleaning of non-product contact surfaces and monitoring of air within the manufacturing area in order to demonstrate the effectiveness of control measures against airborne contamination. Both of these chapters went into effect in March 2015.

Denk said that while Chapter 5 requires manufacturers to verify the cleaning of these surfaces, there was no guidance on assessing these risks. He said that 90 percent of the time these products don't touch anything except for tubing.

Denk said that two years ago, he approached his colleagues about trying to set and meet these limits. He said that "there is no information out there on how to deal with high potent substances for non-product contact surfaces." A group of pharmaceutical industry officials, comprising representatives from Roche, Takeda Pharmaceutical Co. Ltd., Boehringer Ingelheim GMBH, and Novartis AG, a regulator from Germany, and Denk set about to devise thresholds or limits for non-contact surfaces.

The group subsequently published a paper in the Nov. 6 issue of the Parenteral Drug Association's PDA Letter called "Isolator Surfaces and Contamination Risks to Personnel and Patient," which establishes limits for airborne API inside the isolator after cleaning, limits for public surfaces with the possibility of unprotected hand contact, and limits for surfaces with no direct product contact inside the isolator. These limits are driven by occupational health criteria as well as GMP criteria.

Denk said that "we thought we have to get these values out there."

From the editors of the Gold Sheet.

Additional Publications

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PDA Letter

www.pda.org/pdaletter November 6, 2017

Isolator Surfaces and Contamination Risks to Personnel and Patient

PDA Letter

pharmind

Vermeidung der Kreuzkontamination

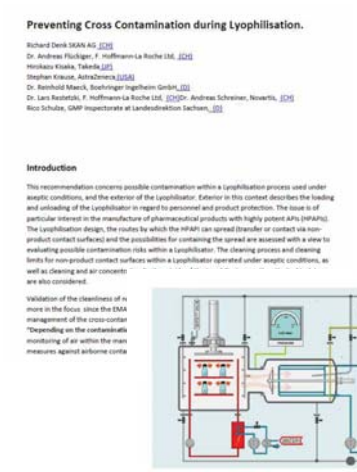
PDA Letter/German translation

PDA Letter 掲載論文「アイソレータ内表面の作業者、並びに患者に対する汚染リスク (Isolator Surfaces and Contamination Risks to Personnel Nov 6, 2017)」の要点

Summary article of the PDA letter to JP Pharmaceutical Magazine

Additional Publications

Cleaning during Lyophilization


Preventing Cross Contamination during Lyophilisation.

Introduction


It is a requirement from the occupational health perspective that exposure to chemicals (API) be primarily controlled by engineering measures and not by the use of personal protective equipment.


Table 01. Proposed EH&S and GMP surface limits for non-product contact surfaces inside an Lyophilisator with the assumption of above closed loading and unloading of the Lyophilisator with isolator technology.

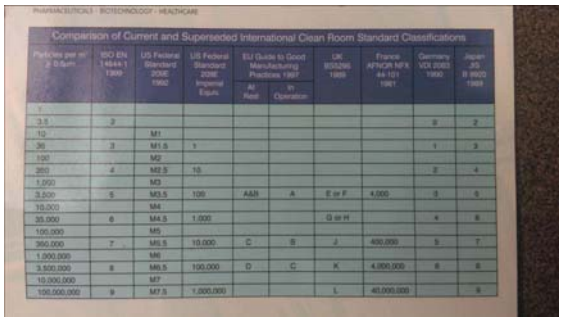
PDA Publication/End of the year

Occupational Hygienic Validation

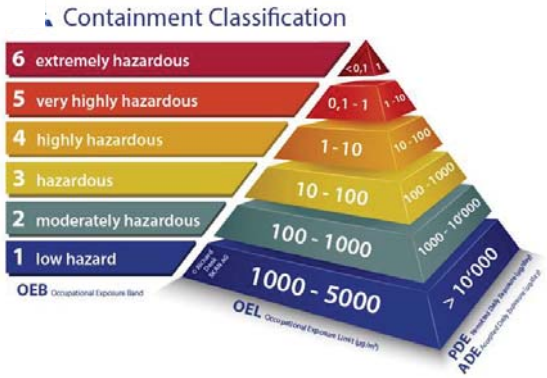
1	Explanation Occupational Hygienic Validation	
2	Occupational Hygienic Validation on Filling Lines	
	2.1	Explanation of the filling line
	2.2	PDE/OEL Requirements
	2.3	Method of the Containment Performance
	2.4	Surrogate Test Product
	2.5	Risk Assessment
	2.6	Used Containment Barrier
	2.7	Location of the Air Samplers and Wipe Positions
	2.8	Training and Good Housekeeping
	2.9	Execution of the Occupational Hygiene Validation
	2.10	Results / Deviation
3	Q&A	

Occupational Hygiene Validation

GMP Requirements



Non GMP Requirements



Occupational Hygiene Validation

What does OEL/OEB mean?

»OEL (Occupational Exposure Limit)

Defines an average concentration load of a drug or API measured over a particular time.

The measurement is carried out in the employee´s breathing area over a period of eight hours (40 hour week). The term OEL comes from the pharmaceutical industry, where internal occupational exposure limits have been calculated for a long time without being regulated by the authorities.

»OEB (Occupational Exposure Band)

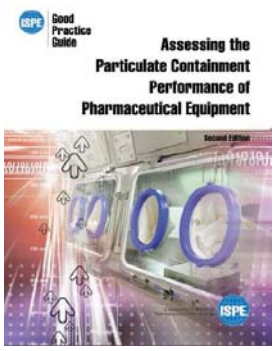
It considers the toxicology of the pure substance. The aim is to provide a system categorisation that can be used to select a suitable production facility and working procedure for a product.

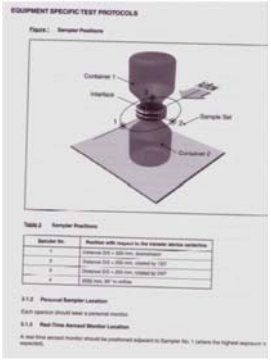
How to measure the Particle Exposure

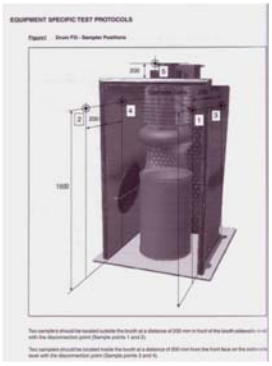
Occupational Hygiene Validation

SMEPAC Good Practise Guide

- **SMEPAC** (Standardized Measurement of Equipment Particulate Containment)



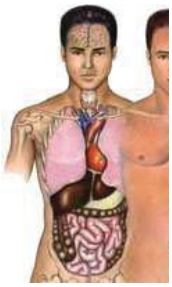


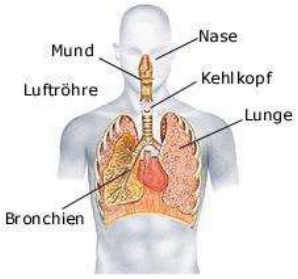


Occupational Hygiene Validation

Absorption through the Operator

- Respiratory ways
- Skin / Hand
- Mucous Membranes

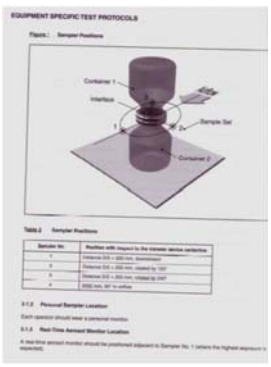


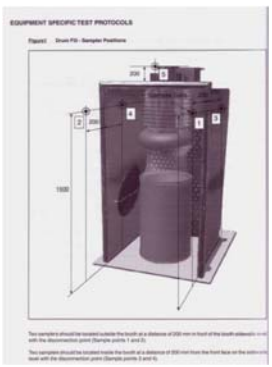


Occupational Hygiene Validation

SMEPAC Good Practise Guide

- **SMEPAC** Does not cover Aseptic Processing. New Methode is needed!



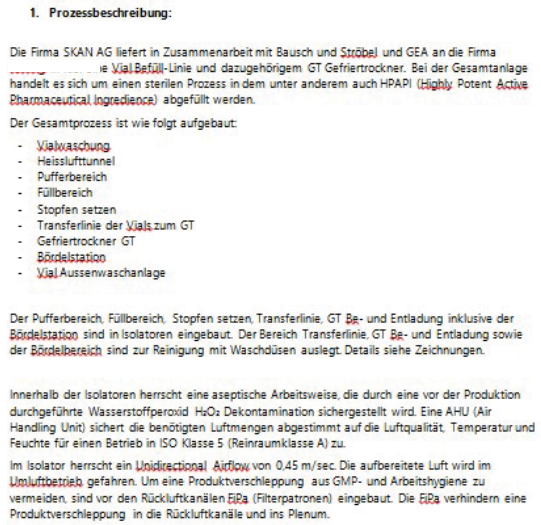


Occupational Hygiene Validation

Explanation of the filling line

Use of the Filling Line.

- Project Team (Customer/SKAN)
- Capacity
- For the use of Vials, Syringes..
- Depyrogenation, Buffer Station, Filling, Stopper, Lyo, Capper, Washer..
- Viable, Non viable Monitoring (Containment Risk)
- Leak rate



1. **Prozessbeschreibung:**

Die Firma SKAN AG liefert in Zusammenarbeit mit Bausch und Ströbel und GEA an die Firma _____ ie Vial Befüll-Linie und dazugehörigem GT Gefriertrockner. Bei der Gesamtanlage handelt es sich um einen sterilen Prozess in dem unter anderem auch HPAPI (Highly Potent Active Pharmaceutical Ingredience) abgefüllt werden.

Der Gesamtprozess ist wie folgt aufgebaut:

- Vialwaschung
- Heisslufttunnel
- Pufferbereich
- Füllbereich
- Stopfen setzen
- Transferlinie der Vials zum GT
- Gefriertrockner GT
- Bördelstation
- Vial Aussenwaschanlage

Der Pufferbereich, Füllbereich, Stopfen setzen, Transferlinie, GT Be- und Entladung inklusive der Bördelstation sind in Isolatoren eingebaut. Der Bereich Transferlinie, GT Be- und Entladung sowie der Bördelbereich sind zur Reinigung mit Waschdüsen auslegt. Details siehe Zeichnungen.

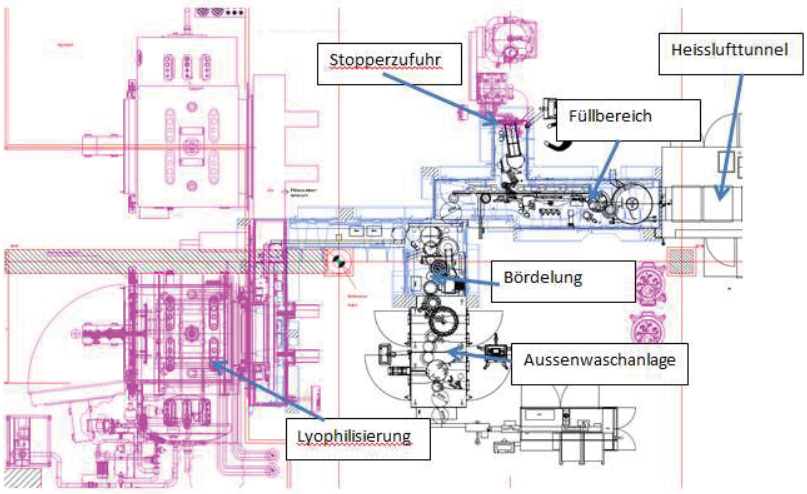
Innerhalb der Isolatoren herrscht eine aseptische Arbeitsweise, die durch eine vor der Produktion durchgeführte Wasserstoffperoxid H_2O_2 Dekontamination sichergestellt wird. Eine AHU (Air Handling Unit) sichert die benötigten Luftmengen abgestimmt auf die Luftqualität, Temperatur und Feuchte für einen Betrieb in ISO Klasse 5 (Reinraumklasse A) zu.

Im Isolator herrscht ein Unidirectional Airflow von 0,45 m/sec. Die aufbereitete Luft wird im Umluftbetrieb gefahren. Um eine Produktverschleppung aus GMP- und Arbeitshygiene zu vermeiden, sind vor den Rückluftkanälen FiPa (Filterpatronen) eingebaut. Die FiPa verhindern eine Produktverschleppung in die Rückluftkanäle und ins Plenum.

Explanation of the filling line

Use of the Filling Line.

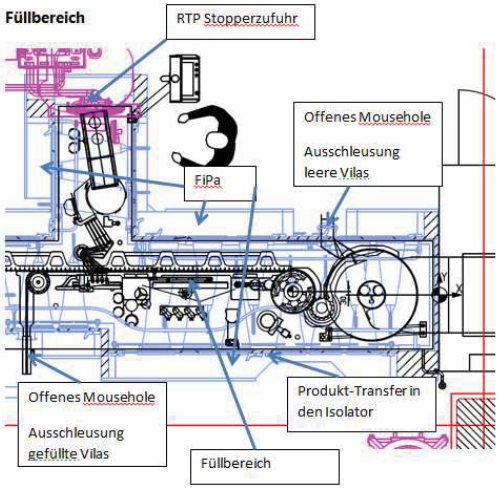
2. Gesamtübersicht



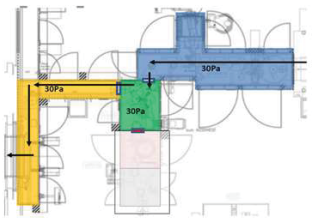
Explanation of the filling line

Use of the Filling Line.

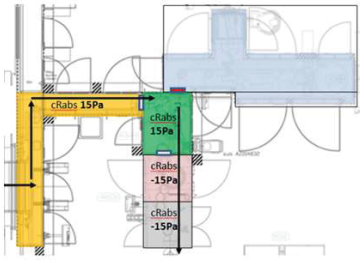
3. Füllbereich



A. Druckkaskaden: Produktion Gefrietrocknerbeladung



B. Druckkaskaden: Produktion Gefriertrocknerentladung



Occupational Hygiene Validation

PDE/OEL Requirements

PDE/OEL Requirements.

- OEL Requirements e.g. 0,1ug/m3
- Safety Factor
- Requirements for the Wipe test

6. Arbeitshygienische Validierung:

Die gesamte Anlage soll für einen Grenzwert OEL (Occupational Exposure Limit) von kleiner gleich 100Ng/m3 ausgelegt sein. Siehe SKAN Containment Pyramide OEB 6 (Occupational Exposure Band)

Aus GMP Sicht entspricht dies einem PDE (Permitted Daily Exposure) von 1ug/day.

Wischtest: 100Ng auf einer Fläche von 10x10cm

Punkt	PDE „Permitted Daily Exposure" mg/day ADE "Acceptable Daily Exposure" mg/day	OEL „Occupational Exposure Limit" ug/m3	Wischproben 10x10cm in ug	Occupational Safety Factor. Between 10-20% of the OEL 1)
1	0,01 mg/day	0,1ug/m3	0,1ug	0,01 – 0,02ug/m3

1) Bei einem Messergebnis von 10-20 % des geforderten OEL (jährliche Wiederholung)
Bei einem Messergebnis von 20-50 % des geforderten OEL (1/2-jährliche Wiederholung)

Occupational Hygiene Validation

Method of the Containment Performance

Method.

- In accordance to SMEPAC
- Reference/Surrogate material
- Dilution in WFI (API Content)
- Air Samplers IOM (Institute of medicine)
- Surface sampling

Texwipe-Stäbchen

Die Rohdaten (Ergebnisse Analyse, Probenahmevolumen, Umgebungsbedingungen) werden verrechnet und als Konzentrationswert in µg/m³ bzw. µg/dm² für den entsprechenden Messpunkt dargestellt. Das Messergebnis wird mit dem vereinbarten Zielwert (Richt- oder Grenzwert, OEL, OEB) verglichen und beurteilt.

6.1 Angewandte Methodik zur Arbeitshygienischen Validierung:

Da es für die arbeitshygienische Validierung von aseptisch herzustellenden Produkten keine Richtlinie gibt wird der Messaufbau in Anlehnung an den ISPE Good Practice Guide „ Assessing the Particulate Containment Control" Volume 2 und dem Kapitel 7 des ISPE Containment Handbuches aufgebaut. Weitere zusätzliche Massnahmen zur Überprüfung der Gesamtanlage werden anhand einer Risikobetrachtung berücksichtigt

- *Angewandte Messmethodik, Filtersysteme, Umgebungsbedingungen, Schulung Personal, Anlehnung an die SMEPAC Richtlinie und an das ISPE Containment Handbuch.*

6.2 Referenzprodukt:

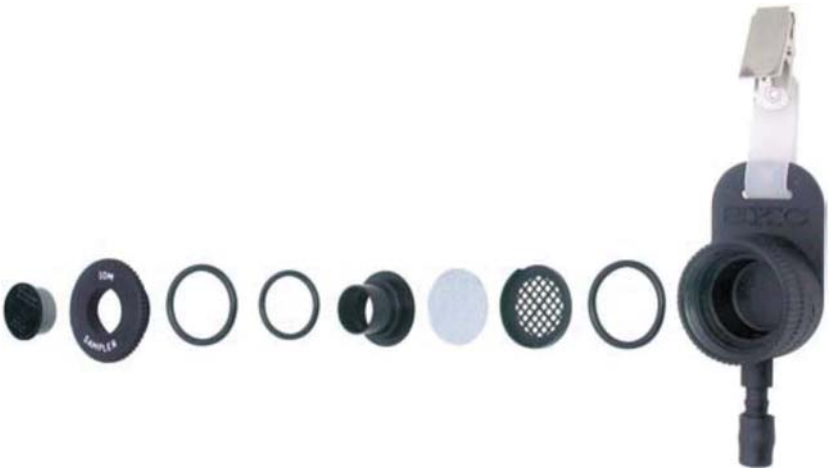
- *Paracetamol/Naproxen oder anderes, Korngrössenverteilung, Mengen, Analytische Auswertung.*
  Lösungsanteil/HPAPI Vialfüllung
  GT Gefriertrockner Entladung Wirkstoffmenge
- *Referenzmenge für die Prüfung festlegen*

6.3 Messverfahren:

Die in die Luft freigesetzten Partikel werden mittels einer kleinen Pumpe auf einem geeignetem Filtermaterial gesammelt. Der Filter wird anschliessend im Analysenlabor so aufbereitet, dass das auf dem Filter gesammelte Produkt mit einer entsprechenden Analysenmethode quantitativ bestimmt wird.

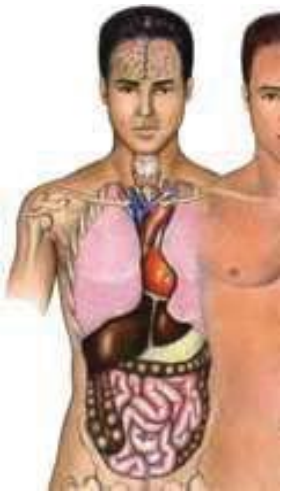
M- Probenahmekopf und Pumpe

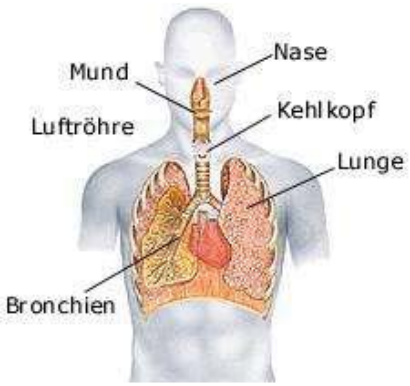
Method of the Containment Performance



Method of the Containment Performance

Airborn Contamination

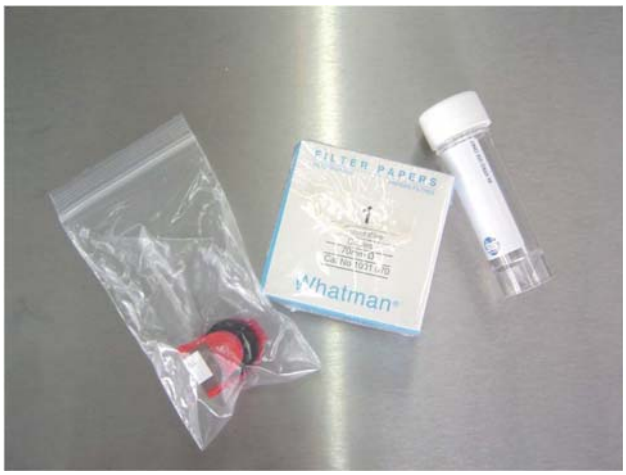




Method of the Containment Performance

Surface Contamination

Method of the Containment Performance



Occupational Hygiene Validation

Surrogate Test Product

Surrogate.

- Suitable to measure low OEL Levels
- Distribution from small to large particle
- Similar to the used product
- Possible use for GMP and Cleaning

6.4 Testprodukt:

Vor den Messungen ist die Testsubstanz zu definieren. Hierbei sind auf folgende Punkte zu achten:

- Produkteigenschaften müssen den Eigenschaften der Testsubstanz möglichst ähnlich sein
- Konzentration der Testlösung im praxisüblichen Bereich (ggf. vorgängig Machbarkeit mit Testsubstanz prüfen)
- Validierte Analysenmethode für Testsubstanz mit entsprechender Bestimmungsgrenze (LOC/LOD), Wiederfindungsrate, Stabilitäts-/Lagerungsdaten (Filter und Probenahmematerial für Oberflächen), Querempfindlichkeiten (Lösungsmittel, Hilfsmittel Rezeptur)

Punkt	Referenzprodukt	Verdünnungsfaktor Füllbereich	Verdünnungsfaktor GT Entladung	Auswahlkriterium
1	Laktose für die arbeits-hygienische Validierung	1/10	1/1	Geeignet zur Verifizierung eines OEL kleiner 100Ng/m3
2	Riboflavin	1/100		Vorab Überprüfung der Substanzausbreitung im Isolator

6.5 Produktionsdauer und Zeitpunkt der arbeitshygienischen Validierung:

Punkt	Max.Produktionsdauer/Charge/ Tage	Start Arbeitshygienische Validierung	Messdauer	Chargen-Nummer
1.	3 Chargen mit Riboflavin-Lösung ohne Zwischenreinigung	xxxx	Komplette Charge	
2.	3 Chargen mit Referenzprodukt ohne Zwischenreinigung	xxx	Komplette Charge	
3			8h	

Surrogate Test Product

Surrogate Substance

- **Powders have different characteristics**

Occupational Hygiene Validation

Risk Assessment

Risk Assessment.

- Customer/Supplier
- SKAN Risk Assessment first
- Additional Risk Assessment with the customer
- Possible Use for GMP and Cleaning
- Can be used as check list before the Work Hygiene Validation

7.0 Risikobetrachtung des Prozesses:

Teilnehmer Risikobetrachtung

Punkt	Teilnehmer	Teilnehmer	Ort	Datum
1.				
2.				

7.1 Produktionsphase: Flüssig Befüllen

Punkt	Containment kritische Bereiche	Prüfung vor der arbeitshygienischen Validierung	Prozesskritische Bereiche für die Positionierung der Luftsampler und Wisch Tests Definieren	EHS Kritisch	GMP Kritisch
1.	Verbindung Schulterring zu Scheibe	Visuelle Prüfung	Prüfung an den Handschuhen die Zugriff zu prozesskritischen Bereichen in der Vialbefüllung	Ja	Ja
2.	Verbindung Armstulpen zu Schulterring	Visuelle Prüfung sowie Prüfung mit Glove Test (Wireless GT)	Prüfung an den Handschuhen die Zugriff zu Prozesskritischen Bereichen in der Vialbefüllung	Ja	Ja
3.	Verbindung Handschuh zu Armstulpen	Visuelle Prüfung sowie Prüfung mit Glove Test (Wireless GT)	Prüfung an den Handschuhen die Zugriff zu prozesskritischen Bereichen in der Vialbefüllung	Ja	Ja
4.	Türdichtung	Visuelle Prüfung/ Anliegen der aufgeblasenen Dichtung		Ja	Ja
5.	Türdichtung Eckradien	Visuelle Prüfung/ Anliegen der aufgeblasenen Dichtung		Ja	Ja
6.	RTP zu Edelstahlwand	Visuelle Prüfung		Ja	Nein
7.	RTP Türdichtung	Visuelle Prüfung		Ja	Nein
8.	RTP beim Abdocken		Prozesskritische RTP prüfen. Beispiel RTP zur Einschleusen des	Ja	Nein

Risk Assessment

			sterilen Endproduktes oder zum Ausschleusen von kontaminierten Material und Proben Probe unterhalb des RTP		
9.	RTP Hydrophobe Filter		Probe am Filter	Ja	Nein
10.	Mouseholes		2 Proben mit Abstand ca. 50 cm und 100cm	Ja	Nein
11.	Bad vial reject		2 Proben mit Abstand ca. 50 cm und 100cm	Ja	Nein
12.	Heisslufttunnel		Probe zur Überwachung der Ausbreitung der Substanz innerhalb des Isolators	Nein	Ja
13.	Kabelverschraubungen		An kritischen Stellen im Füllbereich und beim GT		
14.	Oberhalb CG Verteiler/Im Plenum vor den HEPA Filter		Probe zur Überwachung der Ausbreitung der Substanz innerhalb des Isolators.		Ja
15.	Interner Transport von Prüf und Hilfsmitteln				
16.					

Occupational Hygiene Validation

Used Containment Barrier

Containment Barrier.

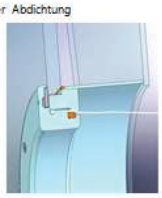
- FiPa
- Glove Ports
- Class Sealing
- Pressure Cascades
- Active mouse holes on critical open areas.

8.2 Eingesetzte Containment Technologien.

FiPa Filter Technologie eingesetzt vor den Rückluftkanälen in allen Sektionen der Isolator-Linie

Die FiPa Filtertechnologie ist ein self contained Filter Technologie, die eine Ausbreitung der hochaktiven Substanz innerhalb des Isolators (durch eine gezielte Luftströmung zu den Filtern) und in die Rückluftkanäle verhindert.

Containment Schulterringe für die Handschuhe mit doppelter Abdichtung



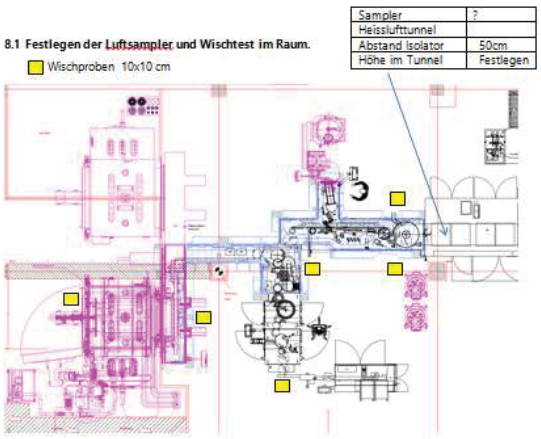
Doppelte Absicherung der Handschuhe an den Schulterringen.

Occupational Hygiene Validation

Air Samplers and Wipe Positions

Air Samplers and Wipe Positions.

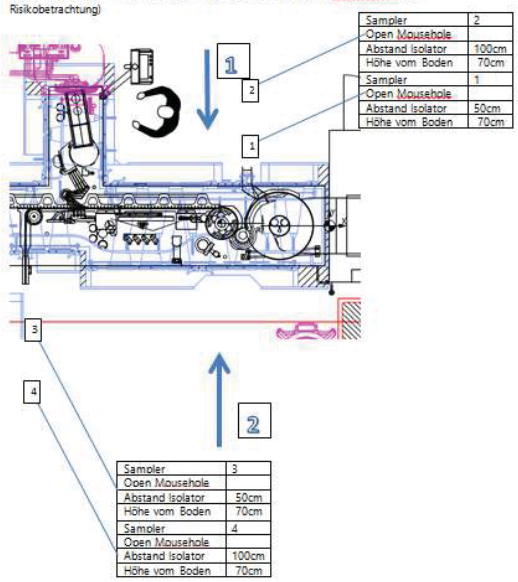
- Learning curve.
- In the beginning more tests to show data
- Based on the risk Assessment
- Operator, Room, Air locks, Corridor
- Together with the customer



Air Samplers and Wipe Positions

8.3 Festlegen der Luftsampler und Wischtest an dem Füllbereich.

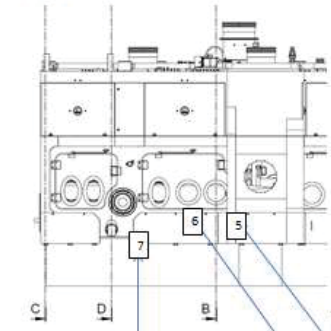
Kritische Bereiche: Heissluft-Tunnel, Füllbereich, RTP und offene Mouseholes (siehe Risikobetrachtung)



Sampler	2
Open Mousehole	
Abstand Isolator	100cm
Höhe vom Boden	70cm
Sampler	1
Open Mousehole	
Abstand Isolator	50cm
Höhe vom Boden	70cm

Sampler	3
Open Mousehole	
Abstand Isolator	50cm
Höhe vom Boden	70cm
Sampler	4
Open Mousehole	
Abstand Isolator	100cm
Höhe vom Boden	70cm

Ansicht 1



Sampler	7
RTP	
Abstand Isolator	0cm
Höhe vom Boden	60cm?

Sampler	5
Abdichtung Tür	
Rechte Seite	
Rundung Ecke	
Sampler	6
Handschuhport	
Neben Schulterring	
ca. 230°	

Air Samplers and Wipe Positions

- **Picture documentation**

Occupational Hygiene Validation

Training and Good Housekeeping

Training and Good Housekeeping.

- Training on the operators
- SOPs on vial breakage
- SOPs on cleaning of spillage
- SOP on unloading the Lyo
- Transfer of contaminated material (Part of the Mock Up already)
- Transfer of possible contaminated viable samplers (short distance)

9.0 Vermeidung der Ausbreitung der Substanz im Isolator „Good Housekeeping":

Punkt	Füllbereich	GT Entladung	Bördelung	Schulung SOP vorhanden.
1	Jeglicher Vialbruch ist über organisatorische Massnahmen zu entfernen.	Jeglicher Vialbruch ist über organisatorische Massnahmen zu entfernen.		
2	Flüssigkeiten müssen sofort mit einem geeigneten Tuch entfernt werden. Kein direkter Kontakt Handschuhe mit der Flüssigkeit.	Bei Vialbruch bei der Entleerung des GT ist die Transportvorrichtung anzuhalten und die Substanz zu entfernen. Auch kontaminierte Vials um den Vialbruch sollten entfernt und aussen gereinigt werden.		
3	Kontaminiertes Glas sowie Reinigungsabfall müssen sofort aus dem Füllbereich über die kürzeste Strecke entfernt werden	Produktverschleppung auf die Transportbänder vermeiden,,		
4	Mögliche Kontaktkontamination überprüfen und entfernen. Auch an Vials die vor und nach dem Vialbruch positioniert waren. Mögliche Kontaminations-	Kontaminiertes Glas sowie Reinigungsabfall müssen sofort aus dem Füllbereich über die kürzeste Strecke entfernt werden		

Work Hygiene Validation

Execution

Execution.

- Supplier/Customer/Industrial Hygienist
- Picture Documentation of the air sampler and position of the wipe test
- Length of the test run and start of air sampling
- 3 Test run
- Short time Exposure Test

10.0 Durchführung Arbeitshygienische Validierung

Teilnehmer Arbeitshygienische Validierung

Punkt	Teilnehmer und dessen Funktion	Teilnehm und dessen Funktion	Schulung an der Anlage erfolgreich abgeschlossen	Datum
1.				
2.				
1.				
1.				
1.				
1.				
1.				
1.				
1.				

12.0 Dokumentation Aufbau der Arebeitshygienischen Validierung an der Anlage

Bildmaterial Aufbau der Luftsampler, Wischproben.

Occupational Hygiene Validation

Results and Deviation

Results and Deviation.

- External Laboratory in the Beginning
- Validated HPLC Method of the surrogate Material
- Calculation of the air born concentration on an 8hrs TWA Time Weighted Average
- Short Time Exposure
- Deviation

Abschliessender Bericht.

Abweichungen

Punkt	Ursache	Massnahme	Verantwortlich	Bis Wann
1	xxx	xxx	xxx	xxx
2	xxx	xxx	xxx	x

Results and Deviation

Example

Table 3: Hecht RTP Charging Assembly, Containment Testing Results (14th April 2005)

Task	Sample Location	Sample Number	Flow Rate (l/min)	Sampling duration (min)	Sample Volume (litres)	Loading (ng)	Atmospheric Concentration (ng/m³)
Test 5: Background before charging	Beside collar that attaches to FIBC	25008446	2.00	41	82.0	10	122
	Beside HEPA port	25008389	2.01	39	78.6	7	87
	On top of control panel	25008398	1.99	40	79.7	9	109
Test 6: Charge 1 (101kg)	Personal – Wolfgang Holzer	25008447	2.00	55	110.2	<5	<45
	Beside glove port	25008457	1.99	55	109.3	<5	<46
	Beside collar that attaches to FIBC	25008408	2.00	55	109.9	<5	<45
	Beside HEPA port	25008385	1.99	55	109.6	<5	<46
	On top of control panel	25008422	2.00	54	107.8	<5	<46
Test 7: Charge 2 (91kg)	Personal – Wolfgang Holzer	25008415	1.99	64	127.4	<5	<39
	Beside glove port	25008410	2.00	65	129.8	7	55
	Beside collar that attaches to FIBC	25008472	2.02	65	131.2	<5	<38
	Beside HEPA port	25008432	1.99	65	129.2	<5	<39
	On top of control panel	25008460	2.01	65	130.9	<5	<38
Test 8: Charge 3 (84kg)	Personal – Wolfgang Holzer	25008465	2.02	48	96.8	<5	<52
	Beside glove port	25008413	2.01	48	96.4	<5	<52
	Beside collar that attaches to FIBC	25008463	2.01	48	96.7	<5	<52
	Beside HEPA port	25008431	1.97	48	94.9	7	70
	On top of control panel	25008474	2.03	48	97.5	<5	<51
						Target Concentration	370

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(English Translation)

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