A Risk Analysis to Establish the Lethality Target for a Novel Aseptic Filler

JOHN W. LARKIN

VP FOOD PROCESS ENGINEERING AND FOOD DEFENSE

IFTPS ANNUAL MEETING 2019 – SAN ANTONIO, TX

IEH
Laboratories &
Consulting Group

Acknowledgement

- MEDInstill Development LLC, New Milford, CT
  - Dr. Daniel Py
  - Dr. Debashis Sahoo
  - Dr. Andreas Toba
  - Dr. David Miller

IEH
Laboratories &
Consulting Group

Outline

1. Description of the aseptic filler
   a. defining the aseptic zone
   b. unique valve/needle and septum
2. Process steps controlling package sterility assurance
3. Risk assessment to determine needle/septum exclusion performance

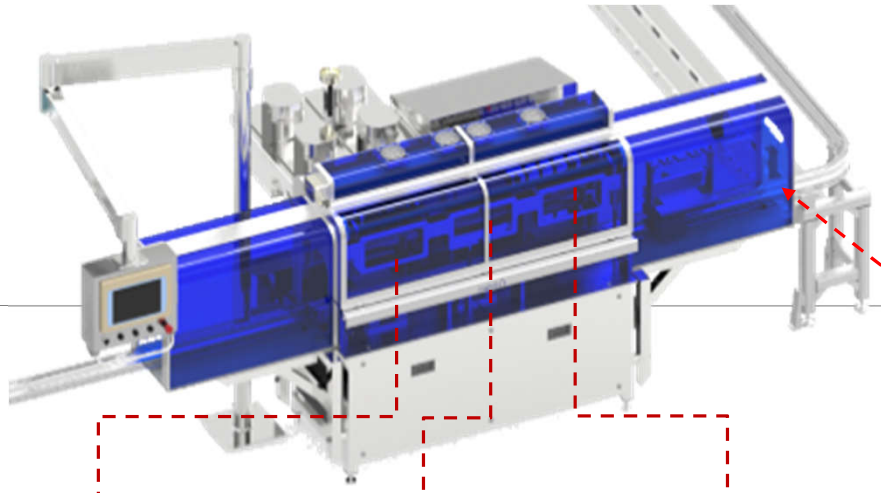
1. Description of Aseptic Filler

MEDInstill Intact^{tm} Filler

- Irradiated sterile containers
- Disposable irradiated sterile tubing and Intact^{tm} needle
- Needle/Septum specially designed
  - functions as a sterile barrier
  - needle/septum interaction = exclusion log reduction
- Aseptic zone is tubing/needle/package

IEH
Laboratories &
Consulting Group

Overview of Process



CONTROLLED AIR OVERPRESSURE ENVIRONMENT

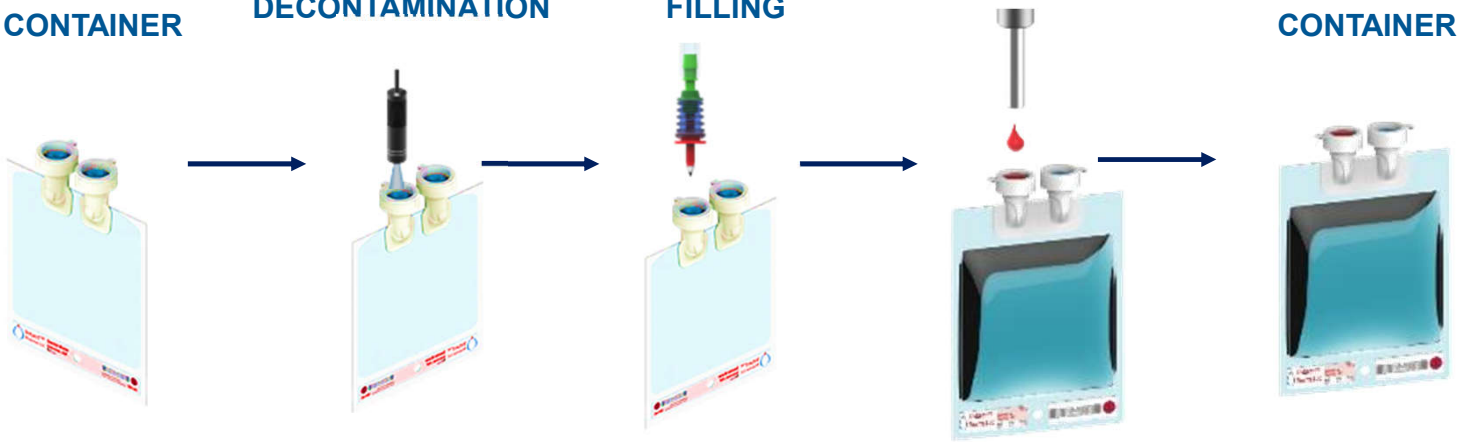
PRE-STERILIZED CLOSED CONTAINER

UV SURFACE DECONTAMINATION

CLOSED TRANSFER FILLING

RE-SEALING

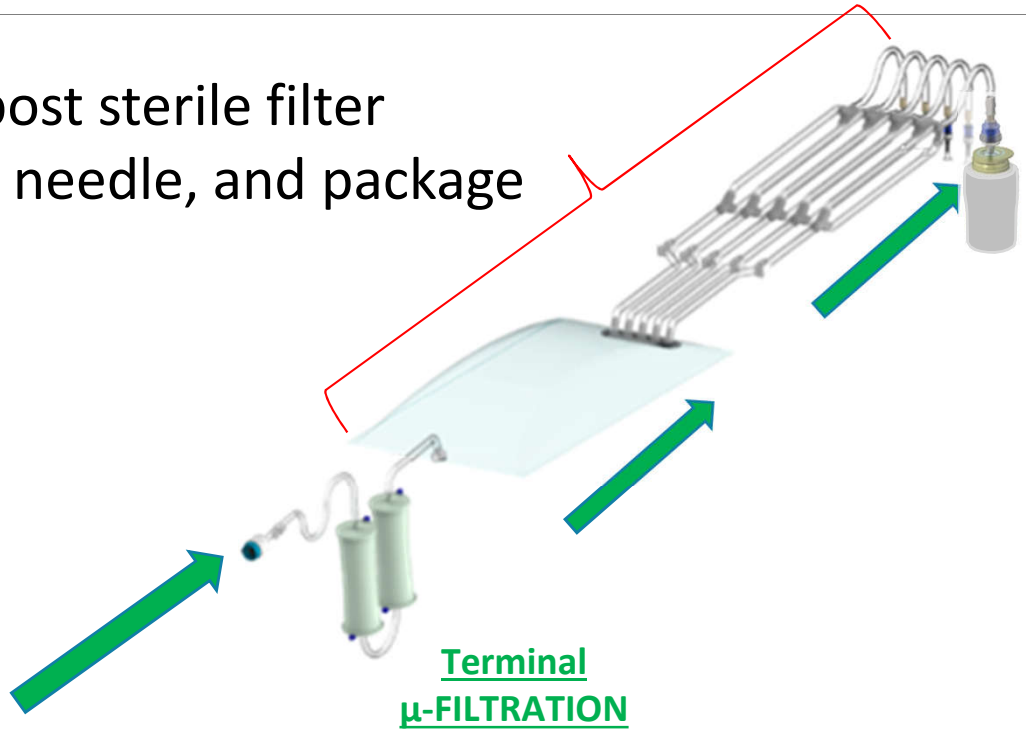
STERILE FILLED CLOSED CONTAINER



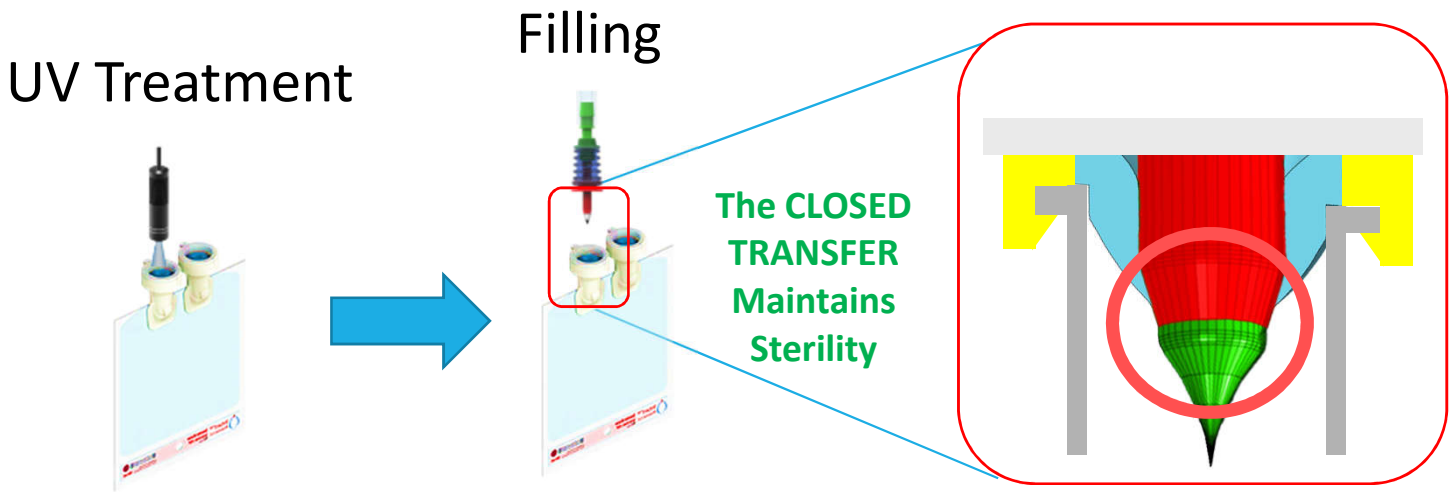
IEH Laboratories & Consulting Group

Aseptic Zone

Aseptic zone – post sterile filter
Includes tubing, needle, and package



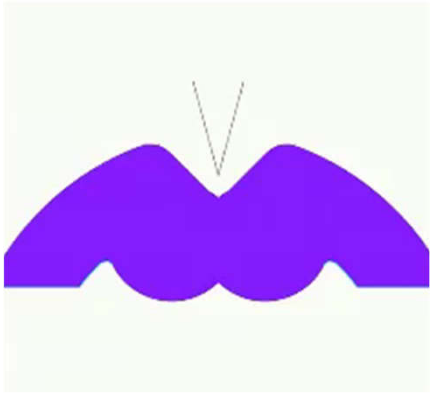
Pre-sterilized Closed Containers are Filled by Piercing Through Self-closing Septum



Piercing through a resealable closure

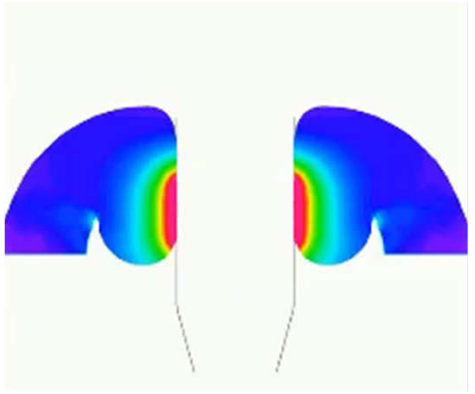
Intact^{tm} Needle/Septum Exclusion

Piercing



STERILE TRANSFER by PIERCING
Internal pressure "wiping wave" as the needle gradually pierces the septum results in mutual surface "sterilization by friction"

Retraction



STERILITY MAINTENANCE upon AUTOMATIC self-closing of both septum and needle:
The doughnut-like elastic under the dome closes before the self-closing dome, resulting in anti-contamination

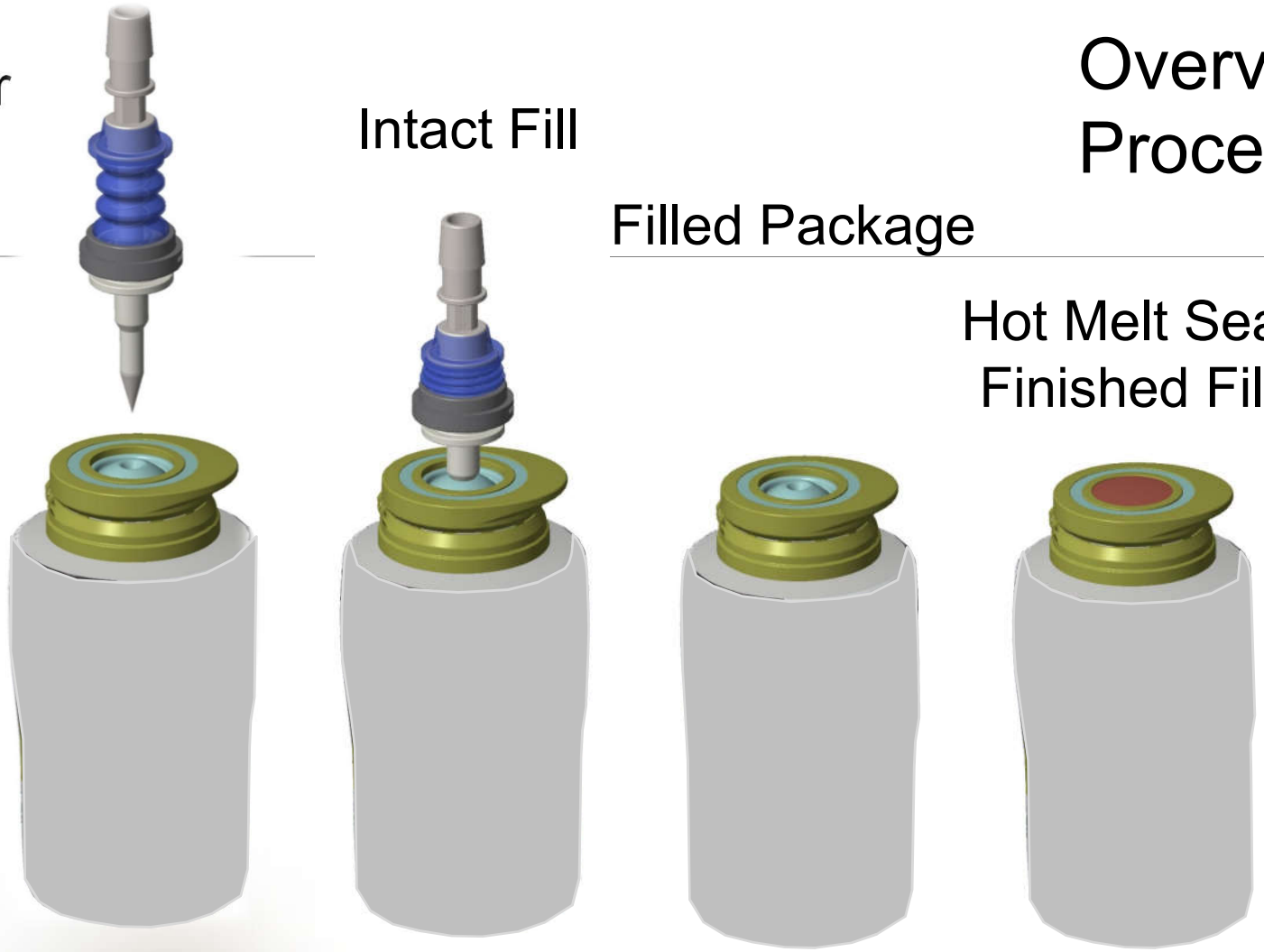
Overview of Process

Ready for Fill

Intact Fill

Filled Package

Hot Melt Seal Finished Fill



http://www.medinstill.com/videos/IFM-FILLER-VIDEO-V6R3-debagging-table-w-drop-box-no-scissors.mp4

2. Process Steps Controlling Package Sterility Assurance

IEH
Laboratories &
Consulting Group

Sterility Assurance Level

- Sterility assurance level = the probability of manufacturing a non-sterile unit/package
- Areas of possible contamination
  - Package removal from sterile outer packaging to treatment by UV lights
  - Transporting of package from UV lights to needle filling

Sterility Assurance Level – (cont'd)

- Process steps controlling package sterility assurance
  i. UV treatment of septum
  ii. Microbial exclusion from needle/septum interaction

3. Risk Assessment to Determine Needle/Septum Exclusion Performance

IEH
Laboratories &
Consulting Group

Summary of Sterility Conditions

- Package and INTACT™ kit are commercially sterile prior to use in the filler
- Package and INTACT™ kit are gamma irradiated > 25 kGy
- Recontamination of package
  - Limited to recontamination from the air
  - Time package is removed from irradiation bag to when filled and sealed (recontamination within the filler environment)
  - Package transport system has HEPA (H14 - %99.995 retention) air overpressure

Recontamination Exposure Factors

- Air microbial recontamination is a factor of:
  - Time
  - Surface area of importance (septum)
  - Microbial concentration within air surrounding the packaging system
  - Settling rate of microbial air contaminates

Recontamination Microbial Risk Model[1]

$$log\ C_{air} + \log v_s + \log At = \log L_c$$

C_{air} = air contamination (cfu/m^3)

v_s = settling rate (m/s)

A = surface area (m^2)

t = time

L_C = contamination load/A

[1]E. D. den Aantrekker, R. R. Beumer, S. J.C. van Gerwen, M. H. Zwietering, M. van Schothorst, R. M. Boom, 2003. Estimating the probability of recontamination via the air using Monte Carlo simulations. International Journal of Food Microbiology 87: 1 – 15.

IEH
Laboratories &
Consulting Group

Bacteria, Yeasts and Molds

- Airborne concentrations (C_{air}) and settling rates (v_s) were collected
  - Literature (12 sources)
  - Food manufacturers (6 factories)
  - Classified into six different product groups reflecting different processing conditions:
    - Dairy group containing solid products
    - Dairy group containing liquid products
    - Dry products group
    - Meat/poultry group
    - Vegetable products group
    - Liquid products group

Air Contamination Load (C_{air})

- Bacteria contaminates (not just pathogens)
  - Group 1: vegetable, liquid and dry products ($\log(C_{air})= 2.44$ cfu/m^3)
  - Group 2: dairy liquid and solids ($\log(C_{air})= 3.19$ cfu/m^3)
  - Group 3: meat and poultry ($\log(C_{air})= 3.39$ cfu/m^3)
- Molds contaminates
  - Group 1: vegetable ($\log(C_{air})= 2.38$ cfu/m^3)
  - Group 2: dairy liquid and solids ($\log(C_{air})= 2.63$ cfu/m^3)
  - Group 3: liquid, dry products, meat and poultry ($\log(C_{air})= 2.88$ cfu/m^3).

Esther D. den Aantrekker, Rijkelt R. Beumer, Suzanne J.C. van Gerwen, Marcel H. Zwietering, Mick van Schothorst, Remko M. Boom, 2003. Estimating the probability of recontamination via the air using Monte Carlo simulations. International Journal of Food Microbiology 87: 1 – 15.

Air Contamination Load (C_{air}) (cont'd)

- High load $\log(C_{air}) = 3.4$ cfu/m^3
- Low load $\log(C_{air}) = 2.4$ cfu/m^3

Esther D. den Aantrekker, Rijkelt R. Beumer, Suzanne J.C. van Gerwen, Marcel H. Zwietering, Mick van Schothorst, Remko M. Boom, 2003. Estimating the probability of recontamination via the air using Monte Carlo simulations. International Journal of Food Microbiology 87: 1 – 15.

Settling Rate v_s

- The settling rate (v_s = 2.70x10^{-3} (m/s)) did not depend on the product or season
- Using this settling rate an average mean particle diameter was determined to be 9.21 (µm)
- Mean diameter is much larger than is exhibited by single cells for most bacteria, yeast in molds

Settling Rate v_s (cont'd)

"This suggests that microorganisms are either attached to each other or to dust or skin particles or water droplets in aerosols, and explains the nonsignificant difference in settling velocities of the microorganisms. This hypothesis is further confirmed by the fact that the airborne concentration increases when cleaning or human activities increase (Hedrick, 1975; Sayeed and Sankaran, 1990)."

Esther D. den Aantrekker, Rijkelt R. Beumer, Suzanne J.C. van Gerwen, Marcel H. Zwietering, Mick van Schothorst, Remko M. Boom, 2003. Estimating the probability of recontamination via the air using Monte Carlo simulations. International Journal of Food Microbiology 87: 1 – 15.

MEDInstill Microbial Settling Model

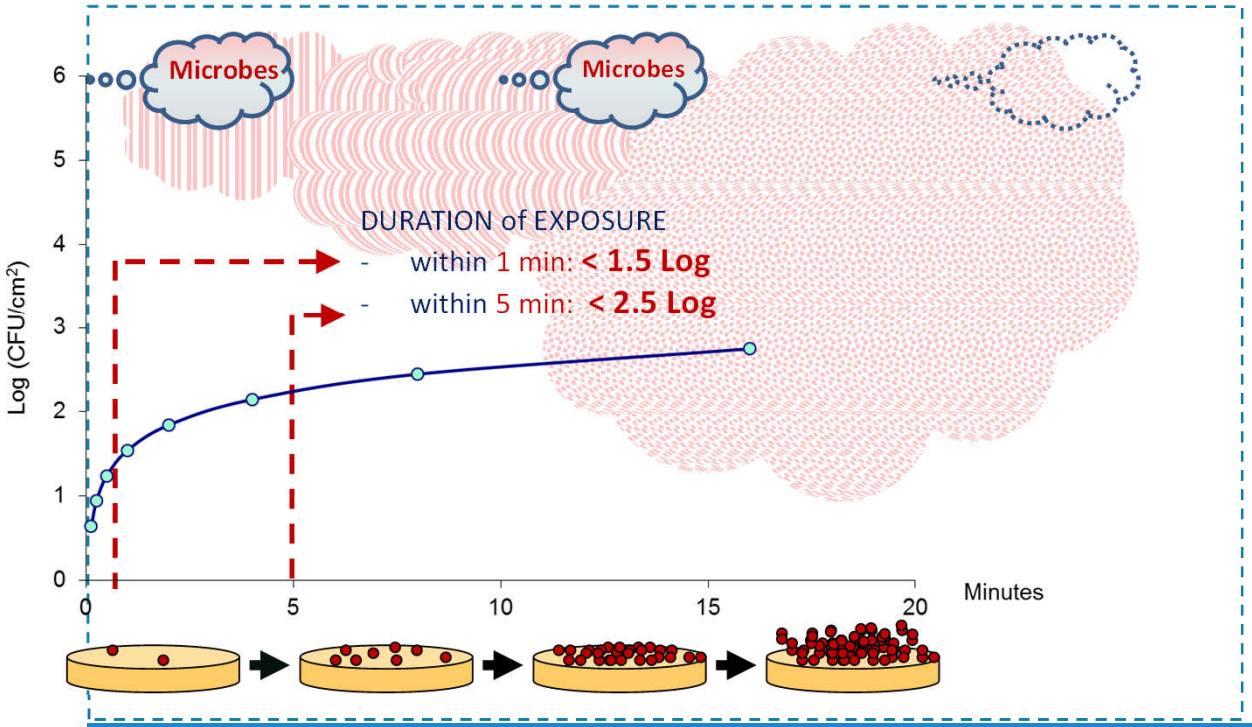
- *Establishing Correlation Between Aerosol and Surface Microbial Populations* by F. Andreas Toba, David A. Miller, Bryan R. Campbell, Debashis Sahoo, James P. Agalloco, and Daniel Py (2018)[1]
- Measured microbial contamination in a simulator
- Their paper settling model:

$$1.037\ log(C_{air}) - 1.3055 = \log(L_C)$$

IEH
Laboratories &
Consulting Group

[1]F. Andreas Toba, David A. Miller, Bryan R. Campbell, Debashis Sahoo, James P. Agalloco, and Daniel Py. 2018. Establishing Correlation Between Aerosol and Surface Microbial Populations. Pharmaceutical Technology. Vol 42 #2, 44-51.

MEDInstill Microbial Settling Model



IEH Laboratories & Consulting Group

MEDInstill Microbial Settling Model (cont'd)

When rearranged

$$1.037\ log\ C_{air} + \log v_s + \log At = \log L_c$$

C_{air} = air contamination (cfu/m^3)

v_s = settling rate (m/s)

A = surface area (m^2)

t = time

L_C = contamination load/A

MEDInstill Microbial Settling Model (cont'd)

- Settling Time (v_s) = 8.25x10^{-4} (m/s)
- Using this settling rate an average mean particle diameter was determined to be 5.09 (µm)
- Smaller than the mean hydraulic diameters determined by den Aantrekker et al. (2003) (v_s = 9.21 µm), but not as small as might be expected for single cells 2-5 µm (den Aantrekker et al., 2003)

Data Published after 2003 Pathogen Loads

- Dobeic et. al (2011) conducted air sampling (158 samples, 30 minute exposure, 1.5 m^3 sample size) within three large slaughter houses and three large meat processing plants
  - No samples positive for *Listeria monocytogenes*
  - Three samples positive for *L. seeligeri* in one of the slaughterhouse
  - Four positive for *L. innocua*, two within one of the slaughter houses and one sample in both a slaughter house and a processing facility.
  - Highest cfu's in areas where aerosolization likely to occur (carcass splitting, washing, evisceration, meat processing, and viscera transport). Total log (cfu/m^3) for the slaughterhouses range around 2.48-2.91.

Data Published after 2003 Pathogen Loads (cont'd)

- Byrne et al. (2008) measured air in a pork processing plant
  - Looked for airborne *Staphylococcus, Listeria and Salmonella* species
  - *Listeria* and *Salmonella* was not detected in any of the samples collected
  - Coliform counts (8 cfu m^3) and *Staphylococcus aureus* counts (8 cfu m^3) were found in the cooking area, blast chill and raw areas respectively
  - Highest total count – $\log(C_{air}) = 2.13 \pm 0.22$
  - Packaging area had total cfu counts of 5 ± 1 cfu/m^3.

IEH
Laboratories &
Consulting Group

Recontamination Calculation

- $\log(C_{air})$= 3.4 cfu/m^3; High risk contamination value across all food processing facility types used by den Aantrekker et al. (2003)
- v_s: settling velocity dependent on the model
- A = 3.14 x 10^{-4} m^2; INTACT™ septum diameter = 2.0 cm
- t (time): two critical limits of 10 minutes and 10 seconds are shaded in grey (*next slide*).
  - 10 minutes: maximum time of package exposure after removal from irradiation bag to UV station
  - 10 seconds: maximum time from UV treatment to needle

IEH
Laboratories &
Consulting Group

Time (min)	den Aantrekker Log(L_C)	den Aantrekker L_C (cfu)	Toba Model Log(L_c)	Toba Model L_C (cfu)
0.16 (10 secs)	-1.68929	0.020450	-2.07852	0.008346
1	-0.89341	0.127815	-1.28263	0.052164
5	-0.19445	0.639077	-0.582657	0.260821
10	0.106583	1.278153	-0.282627	0.521643
15	0.282674	1.91723	-0.106536	0.782464
30	0.583704	3.83446	0.194494	1.564928
60	0.884734	7.66892	0.495524	3.129856
120	1.185764	15.33784	0.796554	6.259713
180	1.361855	23.00676	0.972646	9.389569
240	1.486794	30.67568	1.097585	12.51943

INTACT™ Contamination Loads Pre - UV

- With no air contamination control ($\log(C_{air}) = 3.4$) – L_c of septum $\leq$ 1-2 particles or $\log(L_C) < 0.11$ for exposure times up to 10 mins
- Taking into account an efficiency of only 99.9 % of HEPA filters (H14 rated, >99.995%) - $\log(L_C)$/septum could be < -2.89
- UV treatment delivering > 3.2 log reduction results in a $\log(L_c)$ on the septum after UV treatment of < -6.0. (UV treatment returns septum back to a commercially sterile endpoint)

IEH
Laboratories &
Consulting Group

INTACT™ Contamination Loads (cont'd) Post - UV

- Post UV treatment contamination
  - Commercial sterility of septum after UV treatment
  - At most a 10 seconds exposure between the UV treatment and the INTACT™ filling – $\log(L_c) < -1.6$
  - 3 log reduction in C_{air} from the HEPA filters (H14 rated, >99.995%)
  - Probability of recontamination results in a Log (L_C) < -4.6 (cfu/septum)
- Greater than a 1.4 log exclusion from the INTACT™ filler needle/septum will result in a probability of a non-commercially sterile package of < 1 in a million packages (< 10^{-6})

IEH
Laboratories &
Consulting Group

INTACT™ Contamination Loads (cont'd)

- To meet an expected target non-commercially sterile package of < 1 in a million packages the INTACT™ system was designed to deliver at least a 2 log exclusion.
- When assuming a low air contamination environment, like for vegetable products, a 2 log exclusion from the INTACT™ system would deliver a $<1x10^{-7}$/package sterility assurance.
- Assuming that pathogen loads within air is less than 1% of the cfu's/m^3 the risk from pathogen contamination of the INTACT™ system is < 1×10^{-8} to 1×10^{-9}/package.

IEH
Laboratories &
Consulting Group