

# Decontamination Practices for Plasma Product Facilities

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for  
PPTA TSEWG

- Routine approach for cleaning validation includes mapping for worst case locations and total organic carbon (TOC) analysis
- Cleaning validations involving infectious agents are problematic
  - ✓ the cleaning process has to be scaled down. This in most cases is impossible; e.g. CIP processes, rheologic properties are different on a small scale !
  - ✓ Detection limits are too high to be meaningful
  - ✓ interaction with surfaces: recovery of potentially residual infectivity might be impossible eg.
    - Recovery from swab
    - Use of aggressive reagents to recover the infectious agent may destroy infectivity



Not comparable !

- To study inactivation and/or removal in a cleaning relevant way it would be necessary to be able to detect:
  - ★  $10^{-3}$  IU/mm<sup>2</sup>
  - ★ ~100 molecules PrP<sup>sc</sup>/mm<sup>2</sup>

## Examples of currently used commercial sanitization solutions

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- Sekumatic FSR: commercial brand containing a mixture of NaOH, KOH and hypochlorite, pH 12.5
- Newmatic A and Newmatic D: commercial brand containing primarily a mixture of NaOH, sodium metal silicates and sodium carbonate
- Divosan: peracetic acid based
- CIP-100: Alkaline detergent consisting of potassium hydroxide formulated with surfactant and chelating agents, commercial brand
- Neodisher: FT/KOH containing active Chlorine
- Ikalin: active chlorine NaClO/NaOH

## Most commonly used inactivation solutions or active ingredients

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- NaOH
  - 0.05 to 1.0 M
  - 4° to 65°C
  - 10 min to several hours
- Sodium hypochlorite
  - 100 to 1000 ppm
  - ambient to 45°C
  - 1 to 30 minutes

- Cleaning consists of pre-rinsing followed by sanitization with either NaOH (0.5M) or NaOH / hypochlorite / (detergent) and subsequent rinsing.
- Cleaning validation is performed on product contact equipment
  - ✓ TOC is determined on swab samples
  - ✓ swab samples are taken before and after the cleaning procedure



## Cleaning Procedures: Example 1

	Product	Agent	Conc. (M)	Temp. (°C)	Time (min)
Chromatographic columns	F VIII	NaOH	1.0	22	60
	IVIG	NaOH	0.5	22	60
	F IX	NaOH	1.0	22	60
Tanks	pooling	NaOH	0.15	40	
	fractionation	NaOH	0.15	60	
	CIP	P3 (pH 12)	2%	80	
Ultrafiltration		NaOH	0.15	22	30
			plus 0.1	22	>480

## CIP Procedure

- Step 1. tap water
- Step 2. 0.15 M NaOH, 40°C
- Step 3. tap water
- Step 4. 0.05 M phosphoric acid, 40°C
- Step 5. distilled water
- Step 6. rinse with WFI, 80°C



## Results from cleaning validation (examples)

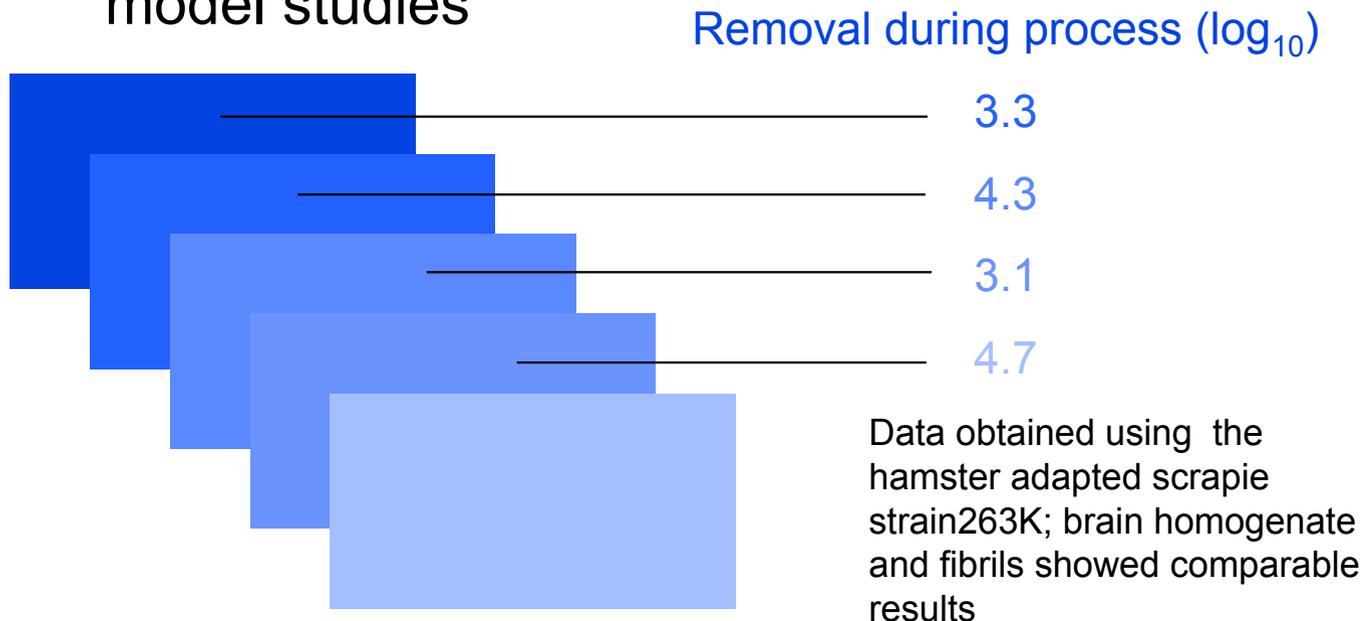
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	Precleaning max [ppm]	Post cleaning [ppm]	Cleaning factor
CIP – Ikalin	381340	< 266	> 1400
CIP - NaOH	263280	< 266	> 990

Cleaning reduces TOC by  
approx. **1000 fold** ( $3 \log_{10}$ )

The limit of detection for the swab sampling / analysis is 266 ppm based on TOC Results of Blank and Environmental Samples for Production Areas

- The manufacturing process of e.g. IvIG (ZLB) can be divided into five modules each one separated from the other by a process step that showed significant reduction of TSE agent in model studies



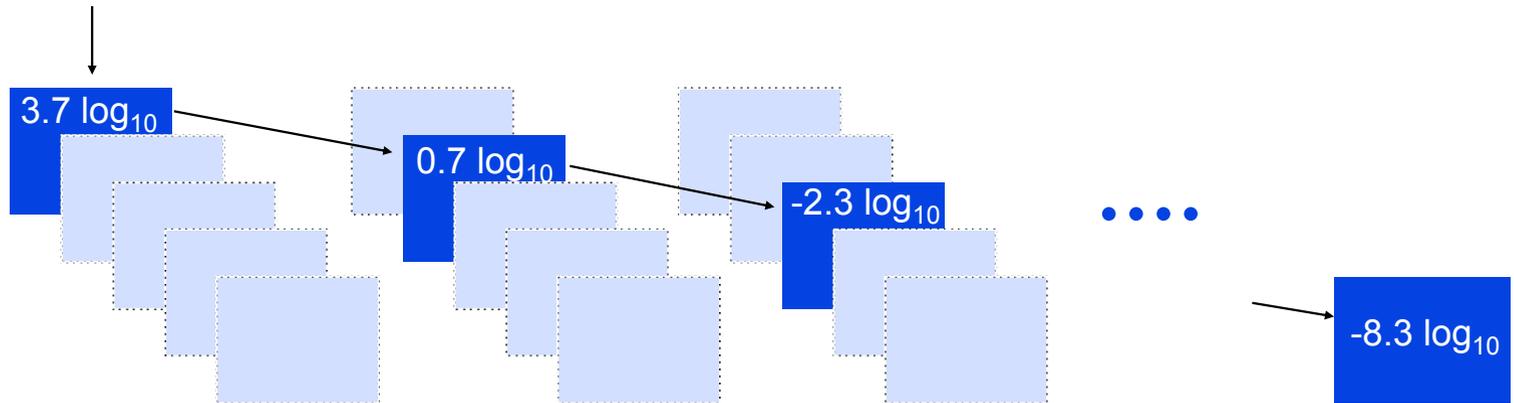
- Facts and assumptions to be made to estimate clearance of TSE by the cleaning procedures
  - ✓ The cleaning process reduces TOC by  $> 3 \log_{10}$
  - ✓ TOC reduction applies proportional to proteins including TSE agents

- A hypothetical case:
  - ✓ It is assumed that a production pool was contaminated with a vCJD donation
  - ✓ The total load of TSE agent then would be 5000 infectious units ( $3.7 \log_{10}$ ) based on the estimation of Brown et al.<sup>1</sup> *that if any TSE agent would be present* in a diseased person it would not exceed 20 IU/mL
  - ✓ All the TSE agent adheres to the surface of module 1 in the production process

<sup>1</sup> Brown et al. Transfusion (1999) **39**, 1169-78

## Estimation of clearance through cleaning

1 vCJD donation  
5000 IU



Cleaning would reduce residual TSE agent by  $3 \log_{10}$  resulting in  $0.7 \log_{10}$  (5 IU) residual TSE agent in module 1

This amount could be carried over into module 2 during manufacturing of the next batch

Making the same assumptions for the remaining modules a total of  $-8.3 \log_{10}$  could end up in a final bulk product

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  - ✓ Making the same assumptions for the remaining modules a total of  $-8.3 \log_{10}$  could end up in a final bulk product
  - ✓ A manufacturing pool of 2000 L plasma results in  $> 8000$  g of IvIG ( $3.9 \log_{10}$ )
  - ✓ Hence, a theoretical, residual amount of  $-12.2 \log_{10}$  or  $6.3 \times 10^{-13}$  IU per g of IgG would result
- This estimate does not take into account a possible inactivation of TSE agents by e.g. NaOH used during cleaning and assumes no clearance by the process!

- It is believed that existing processes in place provide adequate safety.
- Research on the ability of commonly used sanitization fluids has demonstrated rapid destruction of pathogenic PrP.