



# Residues and Implications to the End User

# Why Residues Matter

## Customer Issues

- ◆ **Audit warnings: FDA Form 483**
- ◆ **Safety concerns to personnel: Slippery floors, sticky surfaces**
- ◆ **Health concerns to personnel: Inhalation or skin sensitization**
- ◆ **Corrosion of equipment and materials**
- ◆ **Cleaning of residues require rinsing steps: Cleaning process costly and time-consuming - reduces “productivity” of campaigns**



# Regulatory Impact

On 2/19/2013, I observed white particles on the floor of the clean room. Particles observed were white and approximately two to three millimeters square.

## OBSERVATION 3

Non-microbial contamination was observed in your production area.

Specifically,

On 07/18/2017, I observed that the top metal ceiling grate in the ISO 5 laminar flow hood in the Chemo Room had a reddish-brown residue on the holes of the ceiling grate. This laminar flow hood is used for the production of sterile chemotherapy drug products.

5. Visible signs of debris and residue build-up were observed in the following ISO 5 areas located in the IV Buffer Room:
- underneath the “grate” (return air slots) located on the edge of the LAFW (ISO 5 Hood);
  - on the florescent light cover located on ceiling of LAFW (ISO 5 Hood);
  - around the bolts where the HEPA (b) (4) meets the LAFW (ISO 5 Hood);
  - on and under the (b) (4), used in the (b) (4) process, located on the LAFW (ISO 5 Hood).

February 2017



# Regulatory Impact

6. Visible signs of debris and residue build-up were observed in the following ISO 7 areas located in the IV Buffer Room:
- underneath the supply shelf, located approximately 1½ feet from the LAFW (ISO 5 Hood);
  - on the automatic light switch, located approximately 1½ feet from the LAFW (ISO 5 Hood); and
  - alongside the (b) (4), located approximately 5 inches from the LAFW (ISO 5 Hood).

February 2017

During a walk-through of your facility on 11/27/17 and 11/28/17, we observed the following objectionable conditions during compounding operations in your ISO 5 and 7 environments:

- Rusted metal hinges on plastic totes used to store in-process and finished drug products in your ISO 7 cleanroom
- White film residue on wall surfaces of three of your ISO 5 hoods

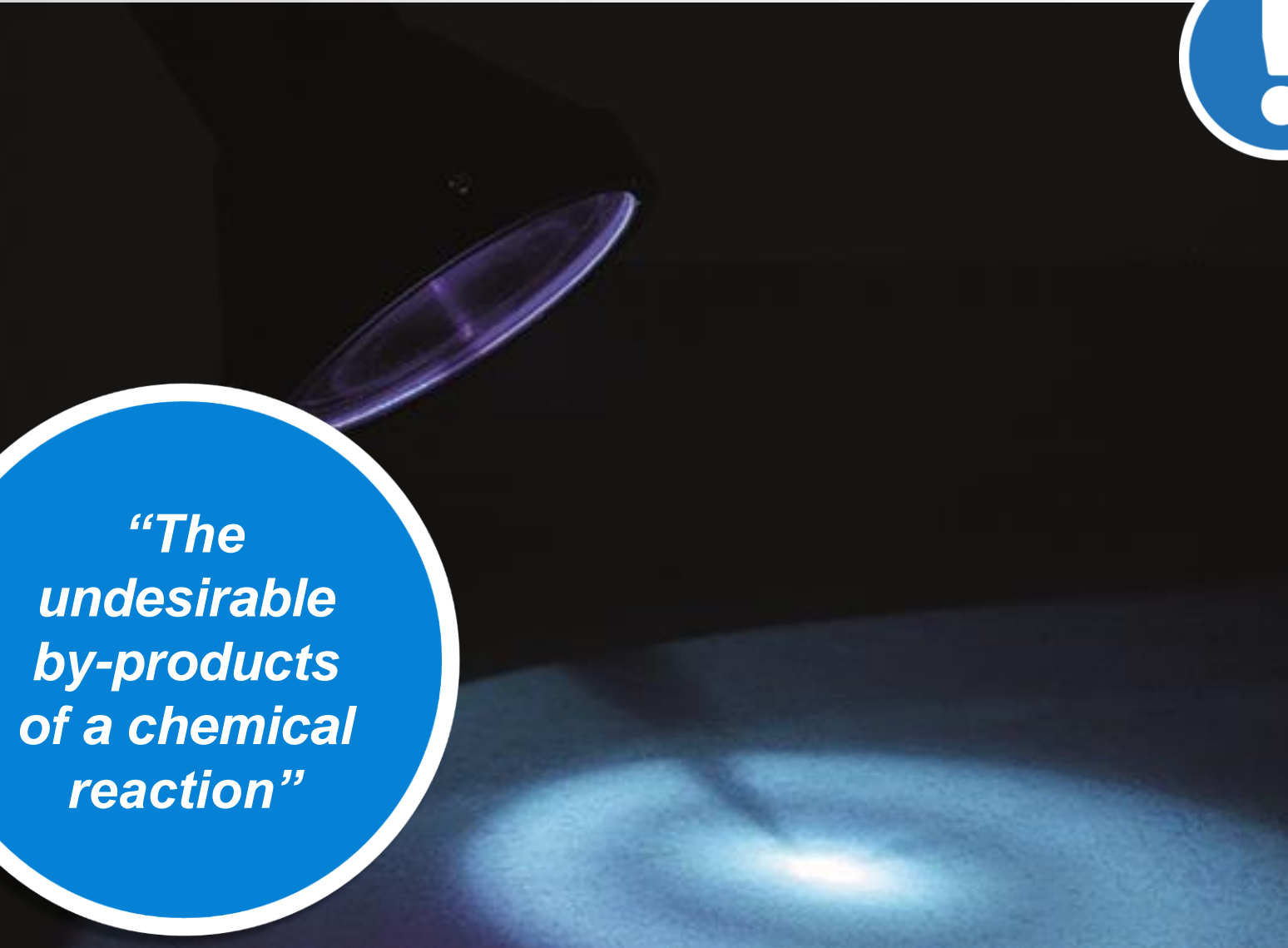
November 2017

# Theoretical Impact



## Risk

- ◆ Interaction between different chemistries
  - ◆ Ineffective in killing microorganisms
  - ◆ EHS
- ◆ Build-up of residues
- ◆ Regulatory questions over the control of cleaning and disinfection
- ◆ Corrosion / damage to surfaces
- ◆ Overcome media neutralization



*“The undesirable by-products of a chemical reaction”*



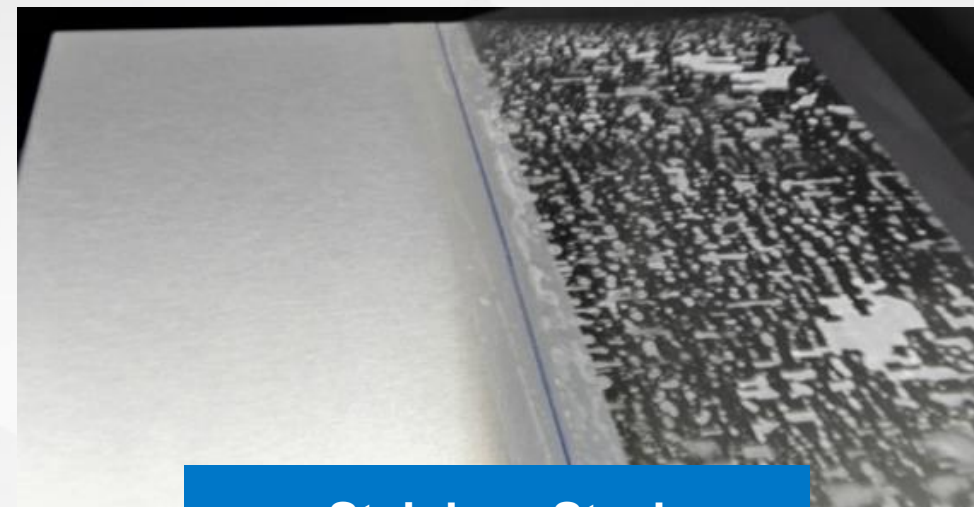
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# Visual Appearance of Residues

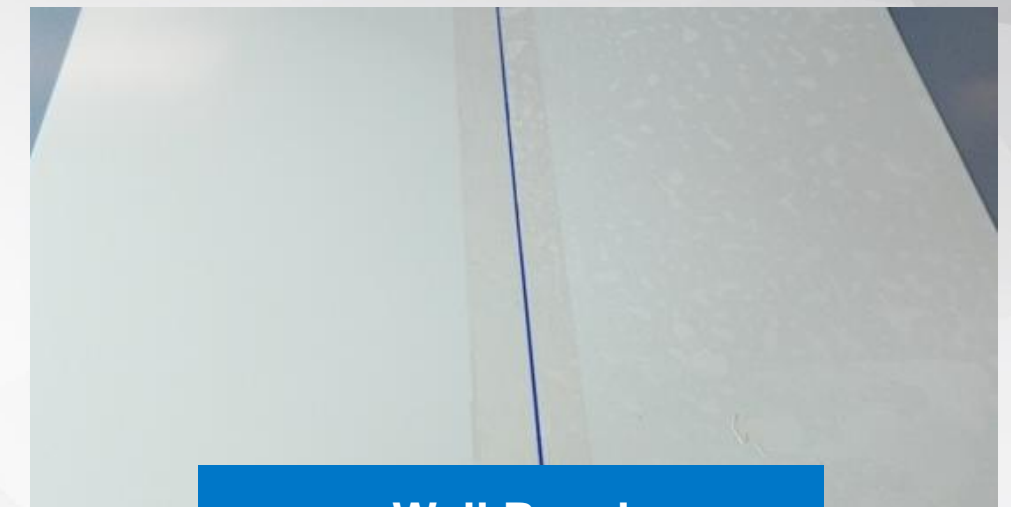
Left side without product | Right side after 10 applications



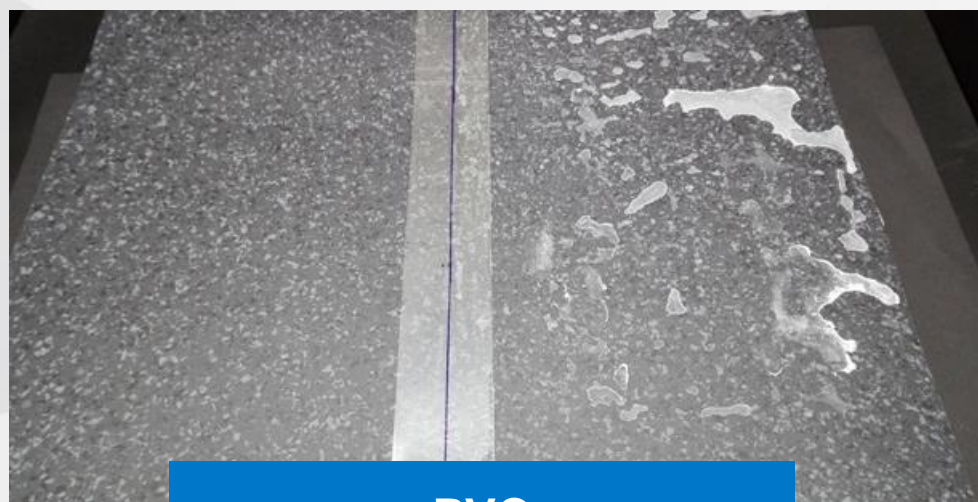
Glass



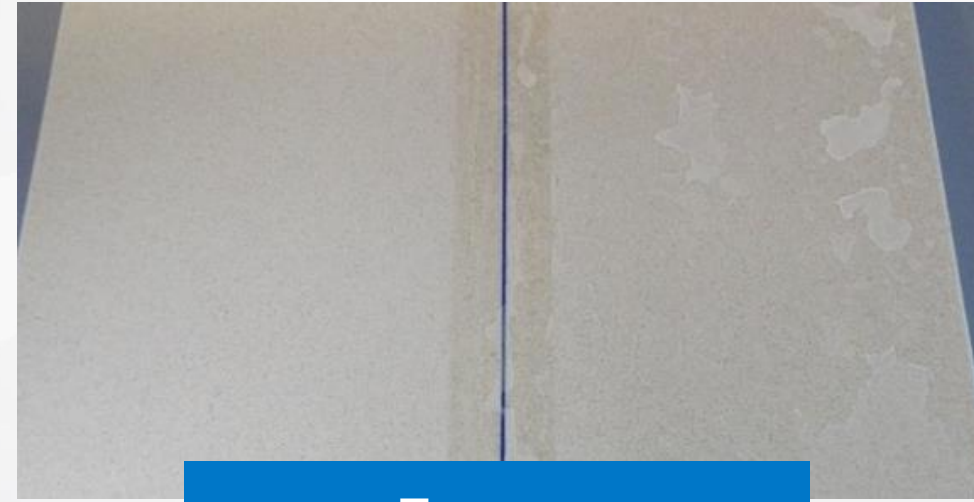
Stainless Steel



Wall Panel



PVC



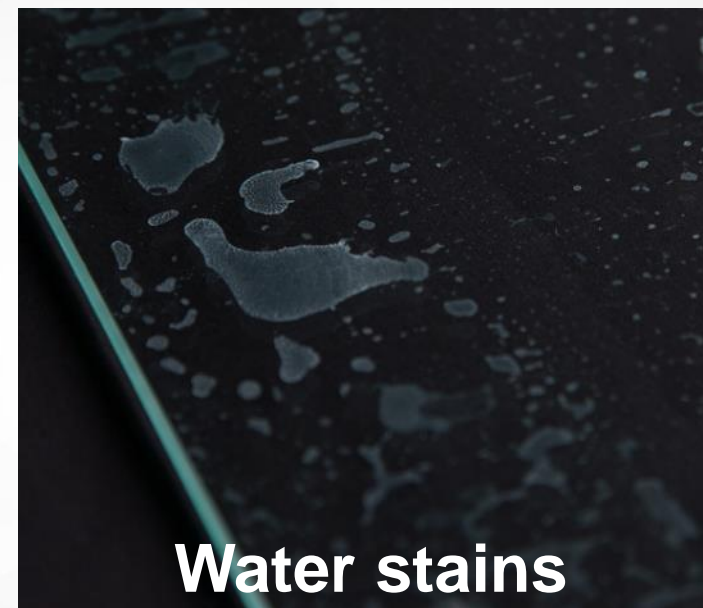
Terrazzo

# Residue Determination in Real Life – “Visually Clean”

## What is a Clean Surface?


- ◆ Residue is a **subjective** measure
- ◆ Depends on: light conditions, surface type, residue type, etc.
- ◆ Residues typically measured as “ppm”:  
1.0% = 10,000 parts per million
- ◆ Golden standard reference “WFI”:  
<0.001 % = <10 ppm = LoD
- ◆ **No residue quantification** in literature existing; low residue = ?? ppm

## Types of Residues





# How Do You Assess “Clean”?



Visually  
clean?

Residue  
measurement?

Micro  
counts?

SOPs?



# Residue Determination – Quantitative Methods

## Scientific Methods and Tools to Determine Residues

- ◆ For residue management, **amount** and **removal** is critical
- ◆ Scientific residue analysis done **QUANTITATIVE** not QUALITATIVE
- ◆ Quantification includes **all ingredients** of the formulation / product
- ◆ Qualification of ingredients requiring specific methods only available for active determination

Accumulation of:

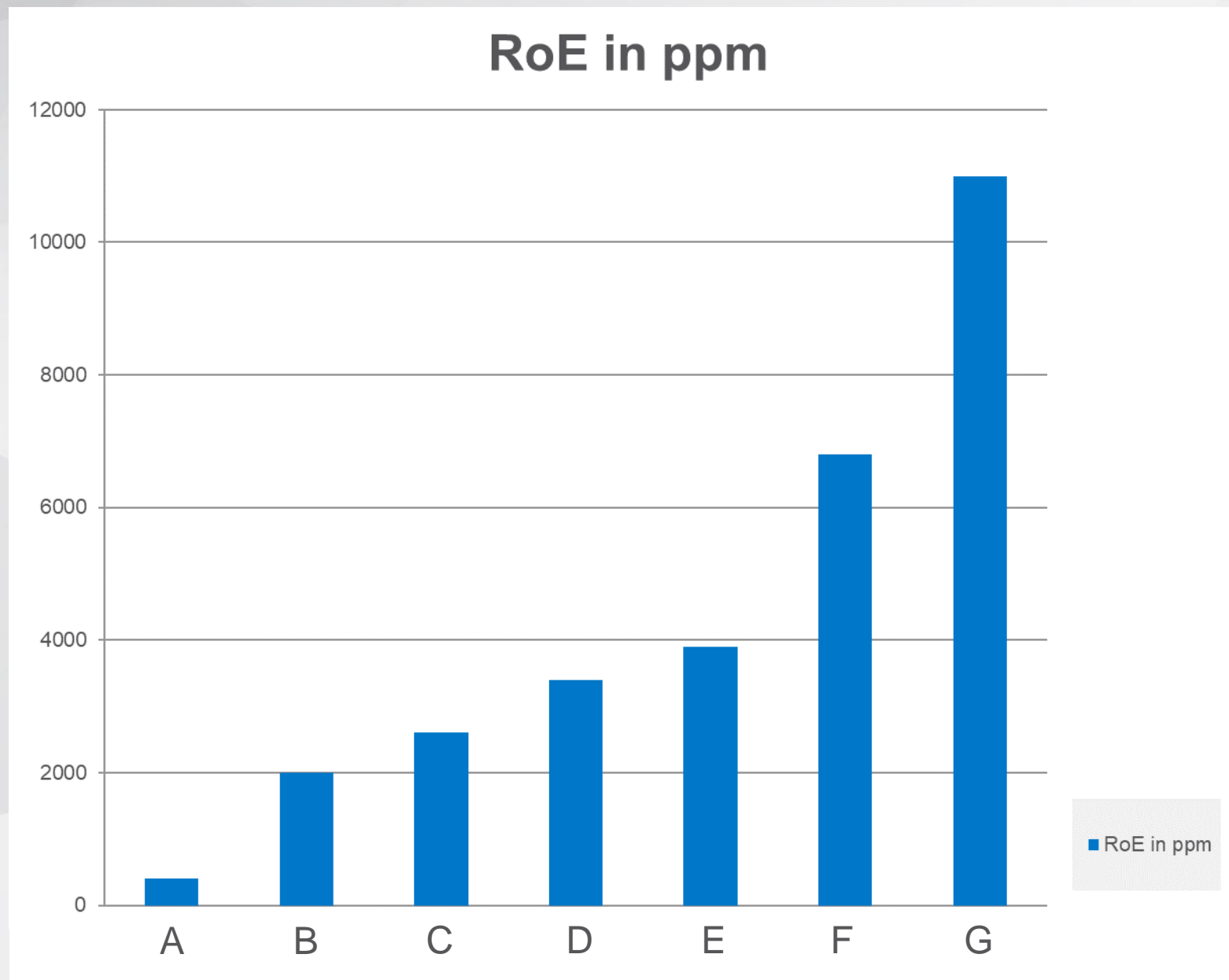
- ◆ Media
- ◆ Buffer
- ◆ Active Substance(s)
- ◆ Stabilizer
- ◆ Activator



*NOTE: Identification of residues important for risk management  
→ PDE values for product contact*

# Comparative Residues (@ Use Conc.)

## Rotational Biocides



Product Name	RoE in ppm	x the Best
A	400	
B	2000	5
C	2600	7
D	3400	9
E	3900	10
F	6800	17
G	11000	28

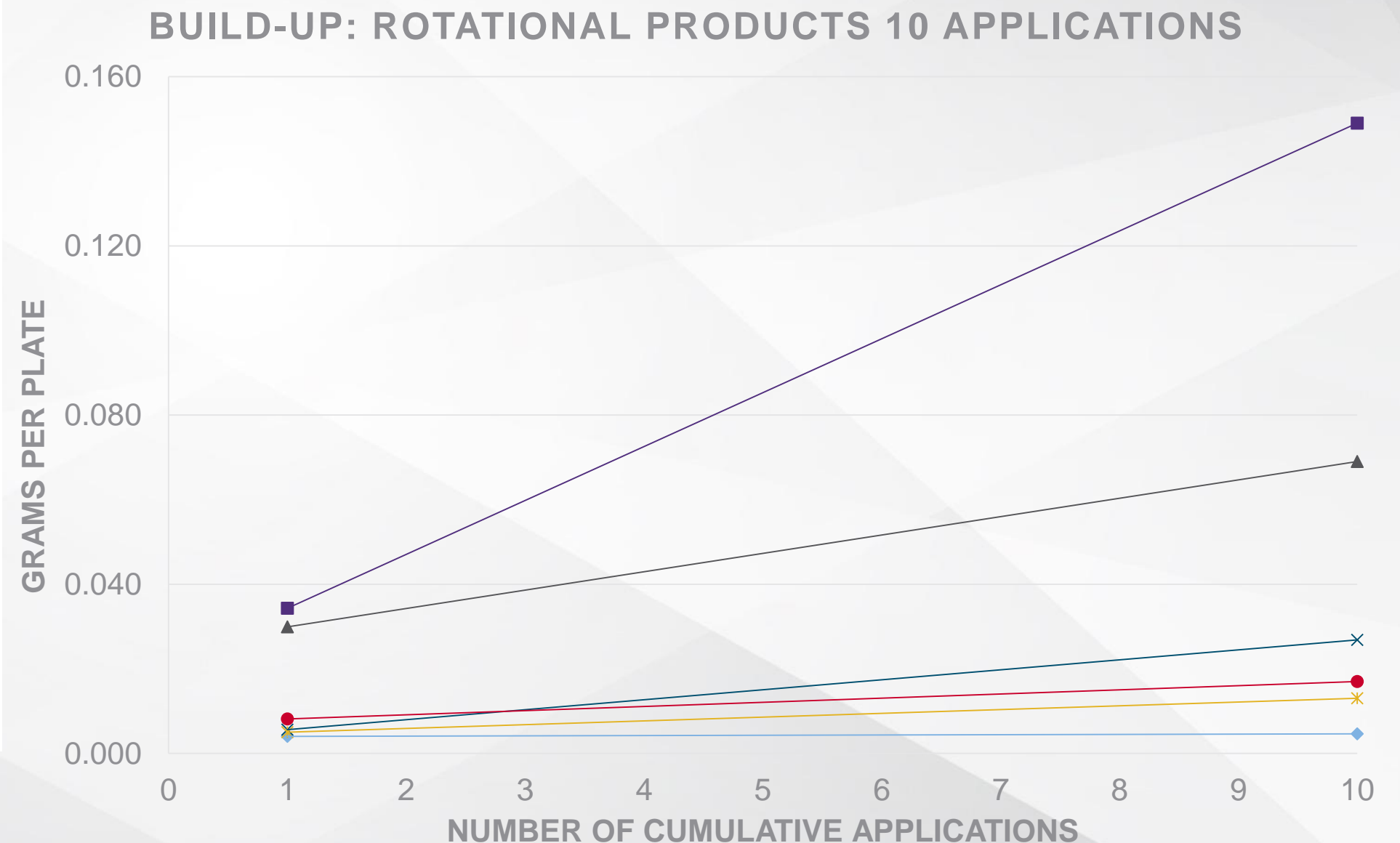
***Residue on evaporation does not correlate to visual***

# Low Residue Concept – Scientific Fundamentals

## Residue Build-up – Successive Applications

### Residue Build-up: Broad Spectrum Products

- ◆ **Successive application** of products or non-efficient removal leads to agglomeration over time
- ◆ Nature of residue (**stickiness**) impacts effect of **accumulation**
- ◆ Equivalent amounts of liquid applied and weight increase measured
- ◆ Graph depicts **broad spectrum rotational** products over 10 applications.





# Cleaning

- ◆ The process of removing residues and soiling from surfaces to the extent that they are visually clean
- ◆ Will slightly reduce the microbial population; will not achieve the same level as a disinfectant
- ◆ Surfaces to be disinfected must be clean
- ◆ Disinfectants can be chemically inactivated by the presence of soiling
- ◆ Soiling can present a physical barrier preventing the disinfectants reaching the microbial cells



## Regulation

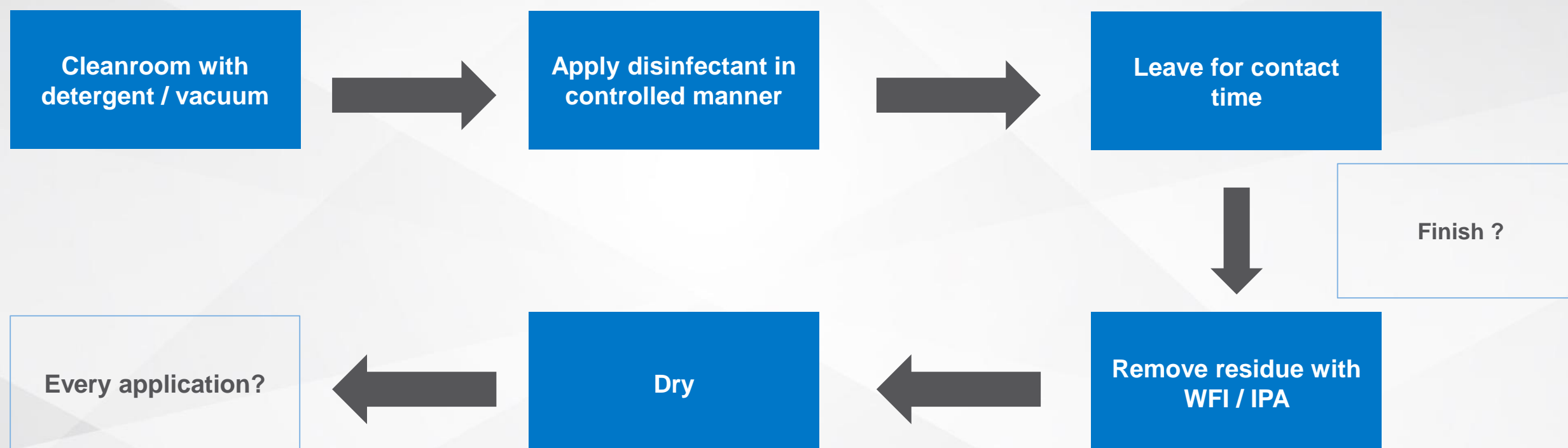
### Annex 1 – Section 5.31 – DRAFT REVISION

*“They (clean areas) should be cleaned and disinfected thoroughly in accordance with a written program **(for disinfection to be effective, cleaning to remove surface contamination must be performed first)** ...**Cleaning programs should be effective in the removal of disinfectant residues**”*

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# Process Flow

## Application & Residue Removal



# Additional Considerations



## Cost of Additional Cleaning

- ◆ Cost of labor, chemicals, training, supplies



## Continued Risk

- ◆ Extended SOPs = increase complexity
- ◆ Risk of non compliance



## Indirect Costs

- ◆ Corrosion or degradation of surfaces.
- ◆ Particle count - EM investigation
- ◆ Remedial cleaning – costly, time consuming and loss of production time



## Productivity

- ◆ Additional hours required for rinsing
- ◆ Lost hours for production



## Compliance / Quality

- ◆ Visual issues
- ◆ Environmental monitoring effect
- ◆ Risk of cross contamination
- ◆ Audit observations



## Health & Safety Risks

- ◆ Slips and falls – sticky floors
- ◆ Volatilization and unfavorable interactions with chemistry



# How Do We Control/Manage Residues?



**Rinsing of surfaces after use of disinfectant chemistries**

**Controlled application of disinfectant to the surface**

**Use of detergent to help break down residues – proactive control with use of a low residue chemistry**

Thank You!