CIP COP

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CIP OPTIMIZATION CASE STUDY

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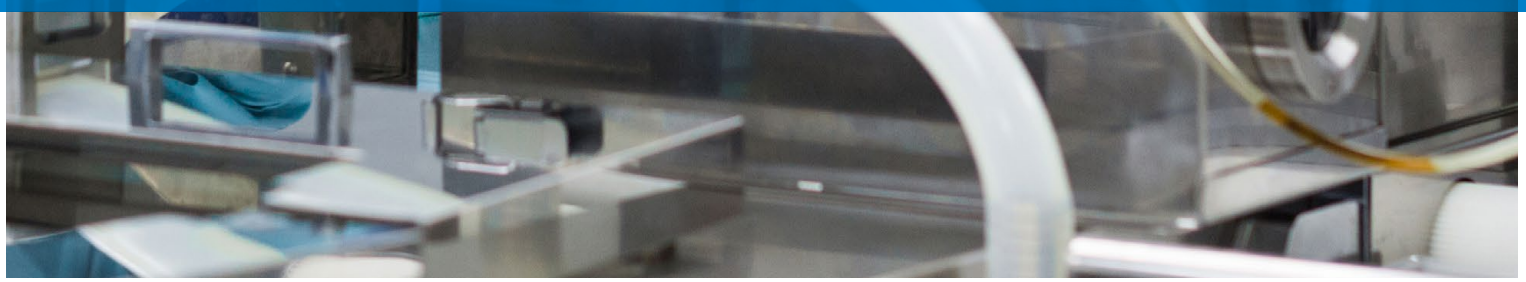


Understanding the **Processes**

'Equipment vendors commonly recommend long cleaning durations because of limited cleaning expertise'

CHALLENGE

With increasing production capacity restraints and expanding sustainability goals, Ecolab has found that pharmaceutical manufacturers can often benefit from evaluating and optimizing their CIP cleaning operations.

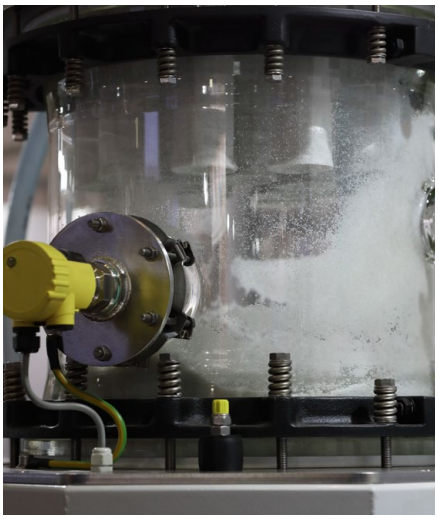
As common practice in the industry, CIP solution volumes and run times are decided via equipment vendor recommendations that include all-purpose detergents.

With these detergents, equipment vendors commonly recommend long cleaning durations because of limited cleaning expertise and opting for the most successful path forward (less cleaning failures and required technical support). This usually entails long cleaning cycles, with reduced production time consequences.

Additionally, validation of their CIP cleaning processes are commonly over 20 years old, are are often complex and convoluted (i.e., multiple add-on confirmation runs, multiple change controls, and outdated CV practices).

In response, manufacturers should evaluate their existing equipment to help uncover opportunities for optimization. This document will cover the typical process for how a drug manufacturer could optimize their granulator.

Process **Background**



When evaluating a facility for optimization improvements, a key step a detergent vendor should take is to gain a full understanding of the production and cleaning process. Below is an example of what a typical process may look like.

MANUFACTURING SITUATION

Industry: Synesthetic actives (small molecule)

Type of manufacturing: oral solid dose

Manufacturing process step: Granulation

Number of grouped products: 8

Product group ADE range: 25 mg to 100 mg per day

Original cleaning validation age: 25 years

Number of validation packages: 5

Change management health: Home Grown (long history over multiple CM systems [paper based and digital])

CLEANING PROCESS

8-hour cycle	Non-specific CIP detergent	7-day DHT	Acid and caustic cleaning steps
Never optimized	Spray devices: static spray balls	Manual intervention prior to CIP	History of aborts and residue build up

CIP RECIPE STEPS

STEP 1	STEP 2	STEP 3	STEP 4	STEP 5	STEP 6
Pre-wash	Non-specific caustic detergent	Post-caustic detergent rinse	Non-specific acidic detergent	Post-acidic detergent rinse	Final rinse

Detergent Provider **Support**

Based on a review of the process on the previous page, Ecolab would recommend a science and risk-based approach to improve efficiency and optimization. Manufacturers should look for a detergent provider partner, like Ecolab, that is able to provide extensive cleaning and cleaning validation support. Other key services to look for from a partner include:

LAB COUPON TESTING

- Specific detergent determination studies
- Worst-case product studies and determination
- Dirty hold time studies (DHT)
- Design of experiments (DoE)

ANALYTICAL METHOD SUPPORT

- Specific or non-specific methods
- Swab or rinse methods
- Full analytical technical support

FIELD SUPPORT

- Site survey and report – optimization and improvements
- Site audit and report – review of legacy cleaning validation program and cleaning procedures

CLEANING VALIDATION

- CV guidance, recommendations, and solutions
- CV supporting documentation
  - PDEs or ADEs
  - Cleaning agent selection studies
  - Product bracketing studies
  - DHT studies

The **Optimization Process**

After a review of the existing process, and utilizing the appropriate technical support, below is an example step by step optimization process that a manufacturer should expect from their detergent provider.

1. Detergent provider conducted a site survey to review the CIP systems and CIP parameter capabilities (i.e., temperature, dosing, and cleaning action) and look for optimization opportunities.
2. Detergent provider and manufacturer reviewed cleaning validation program and create a strategy.
3. The manufacturer submitted soil samples to detergent provider.
4. Detergent provider conducted coupon studies to determine best detergent(s) and sequence.
5. Detergent provider determined worst-case product via detergent solubility testing.
6. Detergent provider conducted DHT studies.
7. Detergent provider conducted DoE studies.
8. Detergent provider supplied the manufacturer with detergent acceptable daily exposure (ADE) values.
9. Detergent provider and the manufacturer reviewed HBEL limit(s) and laboratory capabilities and decided on best analytical method for testing detergent residue.
10. Detergent provider supplied the manufacturer with rinse and swab methods.
11. With detergent provider's technical support, the manufacturer made some CIP engineering design changes.
12. The manufacturer conducted cycle development studies with optimal (DoE) detergent concentration and temperature parameters provided by the detergent provider.

    Testing strategy

    - Visually inspected the granulator after the pre-rinse step to determine volume needed for gross soil removal
    - Took multiple rinse samples throughout the cleaning recirculation step to determine when highest concentration of soil is cleaning solution
    - Reviewed post-caustic rinse step conductivity curve to determine optimal rinse volume
    - Ran final rinse after post-caustic detergent rinse step instead of executing the acidic detergent and post-acidic detergent rinse step
    - Reviewed final rinse step conductivity curve to determine optimal final rinse volume
    - Executed after cleaning testing
13. Reviewed the cycle development sample results.
14. Modified the recipe accordingly.

Conclusion

When working with a detergent provider that is focused on improving efficiency and optimization, such as Ecolab, manufacturers should receive clear achievable outcomes when implementing a new cleaning regime.

The sample results below indicated that each CIP step could be reduced significantly. It was also determined that the acidic detergent step was not needed.

Because laboratory studies determined that acidic detergent does not aide in cleaning, the acidic step only provides insignificant or no passivation effects, and the post-caustic rinse removes the detergent to acceptable levels; the acidic detergent and post-acidic detergent rinse were removed.

Additionally, with the support from Ecolab; The manufacturer was able to remove the manual pre-CIP cleaning step. The CIP can be started without any manual interventions.

Legacy	New	Comments
8-hour CIP cycle	3-hour CIP cycle	Pre-wash, post-caustic detergent rinse, and final rinse were optimized. The caustic detergent recirculation step duration was reduced because the specific detergent solubilized the soil faster and more effectively, and the samples taking determined the optimal time.
Acidic detergent and post-acidic detergent rinse steps	No acidic detergent and post-acidic detergent rinse steps	Acidic detergent and post-acidic detergent rinse were removed because they were not needed.
Manual intervention prior to CIP	No manual interventions required prior to CIP	The manual interventions were not required because of engineering and detergent improvements.
7-day DHT	No DHT	From laboratory coupon studies, it was shown that the length of the dirty hold time did not affect cleanability.
8 products grouped	13 products grouped	Because of the improved cleaning and detergent provider grouping support, the 5 additional hard-to-clean products were added the group.
5 Validation packages	1 Validation package	Re-validated
Change management	1 change	Re-validated
Periodic cleaning failures and aborts	No cleaning failures or aborts	Improved cleaning process

Furthermore, DHT was not required during the cleaning validation; therefore, production time was not significantly affected during validation.

How can **Ecolab** Help?

Ecolab has years of experience of cleaning expertise and performing coupon studies for determining the optimal detergent for hard to clean residues.

We can help:

- Perform a site evaluation to determined optimization possibilities
- Perform a detergent determination coupon study
- Perform a DoE study to determine optimal starting parameters
- Perform a worst-case product assessment
- DHT evaluation (determine affect and necessity)
- Development expert guidance

PARTNER WITH THE EXPERTS

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He earned his bachelor's in chemistry from University of South Florida.

His professional work experience includes over 23 years of cleaning validation while working for Catalent Pharma Solutions, Amylin Pharmaceuticals, Boehringer Ingelheim, Teva Pharmaceutical Industries, Astellas Pharma Technologies Bayer (biotech division), Novo Nordisk, and Ecolab.

He has extensive risk assessment; cleaning development and validation; project start-up; legacy remediation and justification; creating/improving routine monitoring programs; and increasing manufacturing capability experience in small molecule and large molecule API and finished product manufacturing.

He was one of the authors on the new ISPE Guide: Cleaning Validation Lifecycle – Applications, Methods, and Controls and the cleaning validation acceptance criteria chapter lead.

PLEASE SPEAK TO YOUR ECOLAB ACCOUNT MANAGER FOR FURTHER INFORMATION

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