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A Quadro Engineering White Paper

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CLEAN-IN-PLACE MILLS: A CLOSER LOOK AT QUADRO'S U21 HIGH EFFICIENCY COMIL®

Cleaning-in-Place (CIP) is a hygienic cleaning step that is becoming increasingly more common in Pharmaceutical processing equipment for a number of critical reasons. First and foremost – CIP systems are implemented for the health and safety of the end user. Some other benefits include improvements in processing efficiencies and eliminating COP steps – such as handling and transportation of potentially heavy components to and from cleaning rooms. This Paper looks at the governing cGMP guidelines for CIP equipment designs and accepted cleaning methodologies. Finally it takes a closer look at Quadro's CIP validation DoE of the U21 High Efficiency Comil®.

CLEAN-IN-PLACE: WHAT IS ITS PURPOSE?

CIP systems are implemented to safeguard the consumer by removing product residues from equipment by means of a fully or partially automated cleaning process. For decades CIP has been a very common practice in the food, dairy and beverage industries.

In the Pharma industry, there seems to be some confusion as to the exact definition of "CIP". One very clear definition, adopted by Quadro Engineering since it started to offer CIP mills almost two decades ago, is outlined in The Society of Dairy Technology manual (italics added for emphasis):

> "*The cleaning of complete items* of plant or pipeline circuits *without dismantling or opening of the equipment, and with little or no manual involvement on the part of the operator*. The process involves the jetting or spraying of surfaces or circulation of cleaning solutions through the plant under conditions of increased turbulence and flow velocity."[1]

Similarly, the FDA has published its own set of guidelines for the process requirements of CIP equipment. The FDA's Part 211 – Current Good Manufacturing Practices for Finished Pharmaceuticals , section 211.67 "Equipment Cleaning and Maintenance" states:

a) Equipment and utensils shall be cleaned, maintained, and, as appropriate for the nature of the drug, sanitized and/or sterilized at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements.
b) Written procedures shall be established and followed for cleaning and maintenance of equipment, including utensils, used in the manufacture, processing, packing, or holding of a drug product.

In addition, the FDA outlines in its "Guidance for Industry: Manufacturing, Processing, or Holding Active Pharmaceutical Ingredients" the following "Clean-in-Place Methods"[2] :

> "Where feasible, clean in place (CIP) methods should be used to clean process equipment and storage vessels. CIP methods might include fill and soak/agitate systems, solvent refluxing, high impact spray cleaning, spray cleaning by sheeting action, or turbulent flow systems."

Likewise, the European Commission cGMP guidelines make an almost identical recommendation: "The use of 'clean in place' and 'steam in place' ('sterilization in place') systems should be used where possible."[3]

It is important to note that CIP is a cleaning process to prevent contamination or adulteration of drug products.[4] It is not intended to eliminate micro-organisms from the equipment. If the goal is to prevent microbial growth, then the equipment will need to be chemically sanitized or heat sterilized (steamed) after it has been cleaned.

GLOSSARY

CIP:	Clean-in-Place	SIP:	Steam-in-Place
COP:	Clean-off-Place	FDA:	Food and Drug Administration
cGMP:	Current Good Manufacturing Practices	SOP:	Standard Operating Procedures
		FAT:	Factory Acceptance Test
DoE:	Design of Experiments	SAT:	Site Acceptance Test

CLEAN-IN-PLACE cGMP DESIGN AND EQUIPMENT MANUFACTURING GUIDELINES

Significant amounts of documentation and guidelines are available on the design requirements and cleaning steps for CIP processes in the food industry. The European Standard EN 1672-2 (2005), the European Hygienic Design and Engineering Group (EHEDG), and the 3A Authority in the United States being the most prevalent.

All of these guidelines place particular emphasis on the areas in contact with product substances. Thus, manufacturing requirements cover areas such as materials of construction (i.e. 316 and 316L austenitic stainless steels, or alloys such as Hastelloy ,if exposed to high chloride content environments). Product contact surfaces are to be smooth (typically with surface roughness below 0.8 Ra), non-porous and crevice-free. Similarly, there are specific material requirements for all elastomers (i.e. seals and gaskets) – with silicone, Viton and EPDM being fairly common.

Particular attention is to be given to the quality of the welds to ensure they are continuous, smooth and porous-free, and for internal surfaces not to have tight corners or dead areas.[5] For conical mills like Quadro's U21 High Efficiency Comil®, this is achieved by ensuring internal corners inside the milling housing are radiused. This design feature facilitates cleaning by not only preventing the build-up of powders, but also by helping the cleaning fluid to completely remove all residue and facilitate subsequent draining and drying (Figure 1).

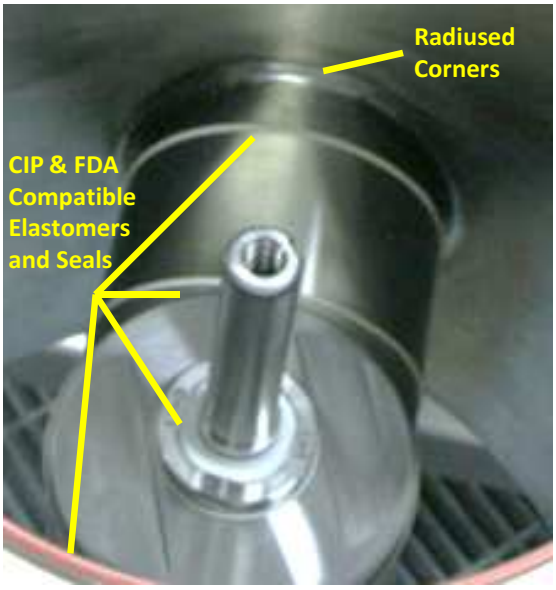

Fig 1: U21 Comil® Gearbox

CLEANING-IN-PLACE: HOW DOES IT WORK?

In addition to the EN 1672-2 (2005), the EHEDG and 3A standards, there are other more pharmaceutical-centric guidelines available from the FDA and from the EU Commission.

The FDA and EU have specific expectations, which include pharmaceutical companies to have written procedures (SOP's) detailing the cleaning processes used, how cleaning processes will be validated and the data collected should support a conclusion that residues have been reduced to an "acceptable level." [4,7] In addition, the cleaning validation protocol should describe the equipment to be cleaned, methods, materials, and extent of cleaning, parameters to be monitored and controlled, and analytical methods.[2]

To achieve the desired results from a CIP process in Pharmaceutical processing equipment, there are some critical parameters that must be controlled during the cleaning cycle. The primary ones being cleaning solution temperature, concentration, contact time, and energy input.[6]

For a CIP process to be successful, the choice of chemicals and the concentration of cleaning agents is dictated by the equipment's materials of construction and to a lesser extent, by the products being cleaned. As outlined previously, the most common contact surface material for pharmaceutical mills is 316 or 316L stainless steel which is very resistant to most cleaning solutions.[8]

CLEANING-IN-PLACE: THE DIFFERENCE IS IN THE DETAILS.

The amount of cleaning liquid volume ("X" lpm flow), the duration of cleaning/circulation ("Y" minutes), and the amount of pressure/turbulence by the spray nozzles (flow rate at "Z" Barg), depends on the characteristics of the powder. Some powders are easier to clean than others, some will be more soluble than others, whereas some powders will tend to build up and pack easier than others; therefore, the cleaning parameters should be set per product.

It is typically during the CIP validation process that the cleaning Standard Operating Procedure (SOP) is developed, under real production conditions, and all the variables are set by the end user. But the vendor of the equipment should be able to provide recommendations and guidelines based on empirical data gathered through a DoE process, successfully proving the repeatable and reproducible cleanability of the equipment.

To this end, Quadro Engineering established a DoE test matrix for the new U21 High Efficiency Comil®. The tests were designed to ensure all product contact surfaces were completely cleaned and the mill would be able to be easily integrated in a Clean-in-Place process.

The industry benchmark for determining and validating complete equipment cleanability is to spray a riboflavin solution on all surfaces to be cleaned. Riboflavin is a vitamin that glows yellow when exposed to a black light or UV-A light (Figure 2).

In December 2007, the VDMA (German Process Plant and Equipment Association), one of the largest and most important industry associations in Europe, published an information sheet on the riboflavin test (Table 1). The document gives advice on agreement, planning, performance and documentation of a fluorescence test.[9]

Fig 2: Riboflavin Solution and UV Light

Fluorescence Test:	Aim of the Test:	Criterion of Quality after the Test
Weak point test	Localizing critical points; optional preliminary stage to the cleanability test	- Visible fluorescence at critical points; these are to be confirmed through a cleanability test
Cleanability test	Verification of full cleanability	- No visible fluorescence under UV light
Optimization test	Optimization and checking suitability of new parameter values through separate, new cleanability tests	- No visible fluorescence under UV light - Improved parameter values (reduced water consumption, shorter cleaning time)

Table 1: Achievable Goals Using Fluorescence Test [9]

CIP DESIGN OF EXPERIMENTS: TEST SET UP AND METHODOLOGY

Quadro Engineering used a solution of 2.5 mg of riboflavin dissolved into 1 liter of hot distilled water (85-90 ^{o}C), then cooled to room temperature and poured into a spray bottle (Figure 2). After spraying the riboflavin solution inside the milling chamber, the unit was exposed to a rinse solution delivered via retractable spray nozzles installed opposite to each other to ensure full overlap coverage (Figure 3).

Twenty two (22) set ups were performed to determine the "weak point test", "cleanability test" and "optimization test" outlined in Table 1. The end goal being to determine the ideal combination of spraying time, liquid flow rates and flow pressures required to consistently remove all traces of the riboflavin solution from the housing, screen and impeller. After each test, black UV light was utilized to identify areas where coverage was insufficient. If there are traces of riboflavin, they will glow green when exposed to black UV light (Figure 4).

Each test was performed by setting up the mill under the same conditions:

1. Thoroughly wash and dry the interior of the U21 Comil®.
2. Visually examine all contact parts on the machine with the UV flashlight. Ensure that there is no green reflected fluorescence prior to proceeding.
3. With the screen and impeller installed and the impeller bolt tightened down, generously spray the interior of the Comil with the riboflavin solution by hand, using the spray bottle. Ensure that all surfaces are wetted with the riboflavin solution.
4. Turn on the U21 Comil® and adjust to the desired test speed.
5. If applicable, spray the chute by applying water pressure to the retractable spray nozzle in the chute.
6. If applicable, spray machine housing by applying water pressure to the two retractable spray nozzles in the machine housing.
7. If applicable, flush water through the Comil by dumping a pail(s) of water into the inlet of the Comil to simulate flush through cleaning.
8. Allow the machine to drain.
9. Turn off the Comil.
10. Carefully remove and visually examine all contact parts on the machine with the UV flashlight, looking for green reflected fluorescence. If green fluorescence is observed, it is an indication of failure of the riboflavin test.

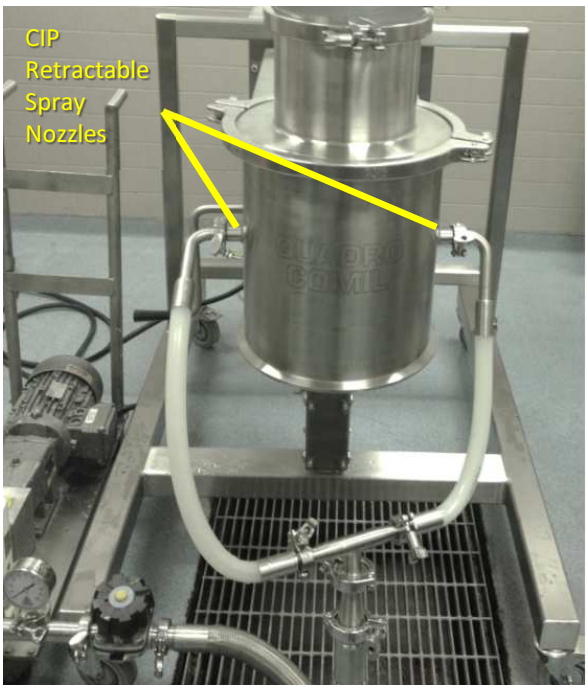

Fig 3: Comil® U21 CIP Test Set Up

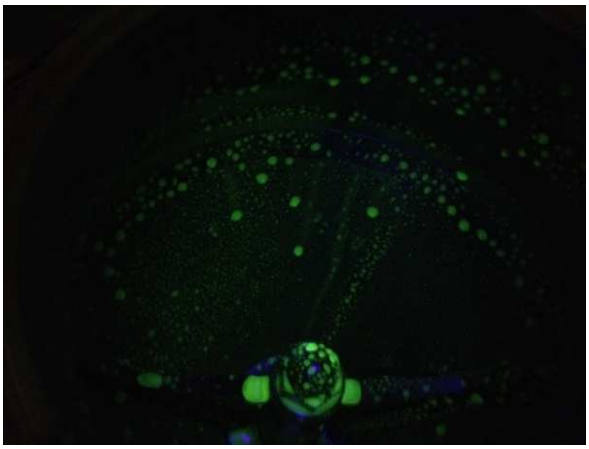

Fig 4: Example of Riboflavin Left In Housing After Cleaning Cycle When Exposed To UV Light

CIP DESIGN OF EXPERIMENTS: RESULTS & DESIGN FEATURES

From the DoE tests, Quadro's U21 High Efficiency Comil® was proven to be suitable for CIP applications and ensuring "no quantity of residue will be visible on the equipment after cleaning procedures are performed."[10]

From its release to the market, the U21 Comil® has successfully passed several CIP Factory and Site Acceptance Tests (FATs & SATs). With its innovative design, the U21 Comil® is a significant advancement to its predecessor, the U20 CIP Comil®. Although the original U20 CIP model met all the CIP requirements, the unit required special impellers and the screens were not interchangeable with non-CIP mills. Furthermore the mill's housings and gearboxes were different from each other.

With the advent of the U21 Comil®, the same screens can be used for CIP and non-CIP applications and the housings/gearboxes have been standardized across both applications. This makes the U21 High Efficiency Comil® significantly more versatile than its predecessors.

Key features of what makes the U21 Comil® CIP design unique include, but are not limited to:

1) Radiused internal surfaces to facilitate liquid solution drainability (Figure 5).
2) Screen's product contact surfaces are isolated by means of opposing O-rings strategically located in the housing and infeed chutes. Thus, product contact surfaces are completely sealed from non-contact areas of the mill (Figure 6). Optimum location and design of the housing/chute O-rings was determined during the "weak point test" stage.
3) Impeller bolt gasket utilizes an exposed PTFE encapsulated O-ring
4) Impeller speed during CIP cycles set to 700 RPM ensures adequate turbulence inside the housing.
5) During the "cleanability test" stage, suitable surface coverage was achieved with two retractable spray nozzles 180 degrees apart. Alternatively, three retractable spray nozzles could be utilized to improve cleaning performance/time. The tradeoff will be an increase in CIP cleaning fluid consumption.

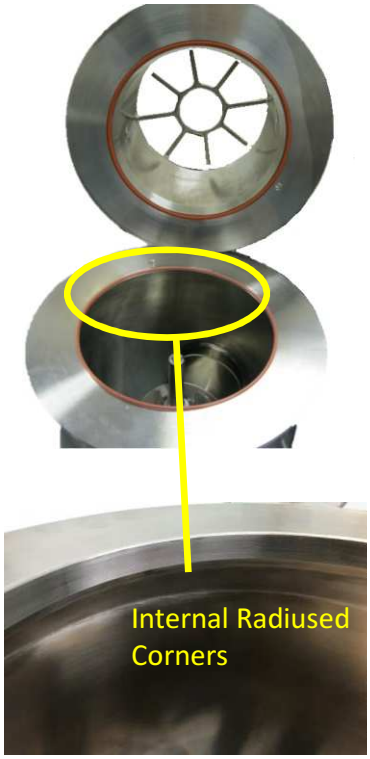

Fig 5: U21 Comil® Housing

Fig 6: Housing O-Ring Detail

6) Optimum cleaning turbulence was achieved when applying the cleaning solution simultaneously to both retractable spray nozzles at 1.8 Barg (26 psig) +/-10%, for a minimum of 20 minutes at a rate of 27 lpm (7 USGPM).
7) Alternatively to using a third nozzle , during the "optimization test" stage, it was proven that flushing from above a minimum of 50 liters of cleaning solution resulted in a pass criteria (i.e. flood feeding from upstream equipment).
8) Redesigned greaseless gearbox (patent-pending). New design eliminates product contamination risks from lubricants should the shaft seal be damaged or worn. A good maintenance program (following the owner's manual recommendations) must be implemented for satisfactory equipment reliability.

Quadro Engineering is pleased to have introduced to the market the U21 High Efficiency Comil®, the latest in hygienic-designed mills. From a combination of DoE tests and customer validated FATs/SATs, Quadro's CIP solution has been proven to be efficient and able to support the increasing safety and cleaning demands expected from Pharmaceutical processing equipment.

ABOUT THE AUTHOR

Wilf Sangüesa, P.Eng. Product Manager – MPT Pharma Processing. Wilf started as the Product Manager for Quadro Engineering in 2005. Over his tenure, he has taken on additional responsibilities, including an expanded role as the Milling Product Manager. In 2014 Wilf was promoted to the role of Product Manager – MPT Pharma, supporting both Quadro and The Fitzpatrick Company and has concurrently been leading the MPT Pharma Marketing Department. He received his Bachelors of Mechanical Engineering from the University of Western Ontario in 1991, and is a member of the Association of Professional Engineers of Ontario (PEO). Wilf started his career serving the Chemical, Petrochemical and Pulp & Paper industries, and has had tenures in industrial material handling equipment and project management. Wilf frequently presents at International Industry and Academia Pharma-focused seminars and conferences, and has a patent pending for the High Efficiency Comil®.

ABOUT MPT PHARMA

Quadro Engineering and The Fitzpatrick Company (IDEX Material Processing Technologies – Pharma Segment) design, manufacture and provide process equipment solutions to the world's top pharmaceutical, chemical and food ingredient processing companies. Through its global operations, Quadro and Fitzpatrick are committed to improve the performance and profitability of its customers' powder processing operations. We achieve this by offering a wide range of products, quality service and leading technology brands, including the Quadro® Comil®, Fitzpatrick's FitzMill™ and Chilsonator®. Our customers are supported by world-leading applications and development experts, and we continually invest in customer-driven innovative solutions to address market needs. We are committed to offering long-term support services through a highly-technical customer service and spare parts network team.

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