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|---|--|-----------------|----------------|
| <b>Case Study Title:</b>                  | <b>Non-Sterile Facility Cleaning Requirements</b>  | <b>Case No.</b> | <b>RMWG-02</b> |
| <b>GMP System Impacted:</b>               | <b>Quality</b>   |                 |                |
| <b>Introduction / Background</b>          | <p>Effective cleaning of non-sterile finished pharmaceutical manufacturing areas is a key component of Good Manufacturing Practices to protect product from extraneous matter, microbiological contamination and product cross contamination. This is commonly accomplished by designing facilities, cleaning procedures and frequencies which effectively take into consideration the activity in the area to be cleaned, the product's microbial susceptibility and the process's inherent dust generation properties. In general, cleaning procedures must be effective in visually removing product residues, extraneous matter and other soil from manufacturing, packaging and warehousing areas. Manufacturing areas should be inspected on a periodic basis and practices should be modified as necessary to ensure areas are maintained in an appropriately clean manner.</p> <p>In this case study, the firm used risk management tools to help define and drive a minimum consistency in cleaning practice and frequency across multiple non-sterile finished pharmaceutical manufacturing departments and operating sites. Prior to conducting the risk assessment exercise, confirmation was made to ensure that core guidance and consistent practices were already in place for cleaning agent selection; cleaning and storage methods for cleaning tools (e.g. mops, etc.); and for facility drain disinfection practices, all of which are fundamental aspects of facility cleaning practices not addressed by this case study.</p> |                 |                |
| <b>Defining the Risk Question</b>         | <p>The risk question developed for the subject case study is:</p> <p style="text-align: center;"><b><i>What is the required level and frequency for cleaning a non-sterile finished pharmaceutical GMP manufacturing area <sup>(1)</sup> <sup>(2)</sup>?</i></b></p> <p>(1) Excluded from the scope of this analysis are antibiotics and potent compounds (e.g. steroids, hazardous compounds, etc.) which generally present with an additional level of exposure and/or cross-contamination concerns and warrant additional cleaning efforts.</p> <p>(2) This analysis is specific to facility cleaning and excludes cleaning of equipment (internal or external surfaces).</p>   |                 |                |
| <b>Selecting a Risk Assessment Method</b> | <p>The effort first required the compilation of empirical information to gather and organize the risk inputs. The risk tool selected for this purpose was:</p> <p style="text-align: center;"><b>Prioritization Table</b></p> <p>After prioritization, a qualitative analysis was performed, based on the product risk prioritization and the process and facility design attributes. The risk tool was:</p> <p style="text-align: center;"><b>Decision Tree</b></p>   |                 |                |

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**Risk Assessment  
(Risk Identification,  
Analysis and  
Evaluation)**

The purpose of the risk assessment was to help prioritize cleaning efforts based on actual process conditions and specific product needs.

Risk prioritization considerations for this analysis included: a review of key product characteristics such as inherent microbial inhibitory / susceptibility characteristics and dust potential (based on historical experience); and the review of key process and facility design attributes such as use of open versus closed manufacturing equipment; use of dedicated versus multi-product operations, and use of cross-contamination barriers (e.g. physical barriers, HVAC, etc.).

A team of industry microbiology subject matter experts worked to categorize cleaning options and developed a prioritization schematic (reference Table 1). The table is used by manufacturing and quality heads to first identify the applicable GMP Area (Manufacturing, Primary Packaging, etc.); then to determine the applicable product category (microbial susceptible and/or dust generating); and finally using the determined GMP area and product category, determine minimum requirements on "what" to clean (e.g. floors, benches, etc.) and "how" to clean (e.g. vacuum / sweep; we clean; and disinfect).

**Table 1 Prioritization Table**

| PRODUCT CATEGORY➔                              | GMP Manufacturing Area |       |       |                   |       |       |                             |       |       | GMP Area (other)        |       |                     |                                |       |
|--|------------------------|-------|-------|-------------------|-------|-------|-----------------------------|-------|-------|-------------------------|-------|---------------------|--------------------------------|-------|
|  | Manufacturing          |       |       | Primary Packaging |       |       | Manufacturing Area Hallways |       |       | Changing Rooms/Stations |       | Secondary Packaging | Shipping & Receiving Warehouse |       |
|  | I                      | II    | III   | I                 | II    | III   | I                           | II    | III   | I                       | II    | III                 |                                |       |
| <b>FLOORS</b>                                  |                        |       |       |                   |       |       |                             |       |       |                         |       |                     |                                |       |
| Vacuum/Sweep                                   | Green                  | Green | Green | Green             | Green | Green | Green                       | Green | Green | Green                   | Green | Green               | Green                          | Green |
| Wet Clean                                      | Green                  | Green | Green | Green             | Green | Green | Green                       | Green | Green | Green                   | Green | Green               | Green                          | Red   |
| Disinfect                                      | Green                  | Green | Green | Red               | Red   | Red   | Green                       | Red   | Red   | Red                     | Red   | Red                 | Red                            | Red   |
| <b>BENCHES</b>                                 |                        |       |       |                   |       |       |                             |       |       |                         |       |                     |                                |       |
| Wet Clean / Disinfect                          | Grey                   | Grey  | Grey  | Grey              | Grey  | Grey  | Green                       | Green | Green | Green                   | Green | Green               | Green                          | Green |
| <b>WALLS &amp; EXTERNAL EQUIPMENT SURFACES</b> |                        |       |       |                   |       |       |                             |       |       |                         |       |                     |                                |       |
| Wet Clean                                      | Green                  | Green | Green | Green             | Green | Green | Green                       | Green | Green | Green                   | Green | Green               | Green                          | Red   |
| Disinfect                                      | Green                  | Red   | Red   | Green             | Red   | Red   | Red                         | Red   | Red   | Red                     | Red   | Red                 | Red                            | Red   |
| <b>CEILINGS</b>                                |                        |       |       |                   |       |       |                             |       |       |                         |       |                     |                                |       |
| Vacuum/Sweep                                   | Green                  | Green | Green | Green             | Green | Green | Green                       | Green | Green | Green                   | Green | Green               | Red                            | Red   |
| Wet Clean                                      | Green                  | Red   | Red   | Red               | Red   | Red   | Red                         | Red   | Red   | Red                     | Red   | Red                 | Red                            | Red   |
| Disinfect                                      | Green                  | Red   | Red   | Red               | Red   | Red   | Red                         | Red   | Red   | Red                     | Red   | Red                 | Red                            | Red   |

|  |
|--|
| <b>PRODUCT CATEGORY</b>  |
| <b>I Microbial Susceptible</b>   |
| <b>II Not Microbial Susceptible &amp; Dust Generating</b>                |
| <b>III Not Microbial Susceptible &amp; Minimal to No Dust Generating</b> |

|       |                       |
|-------|-----------------------|
| Green | See defined frequency |
| Red   | Not required *        |

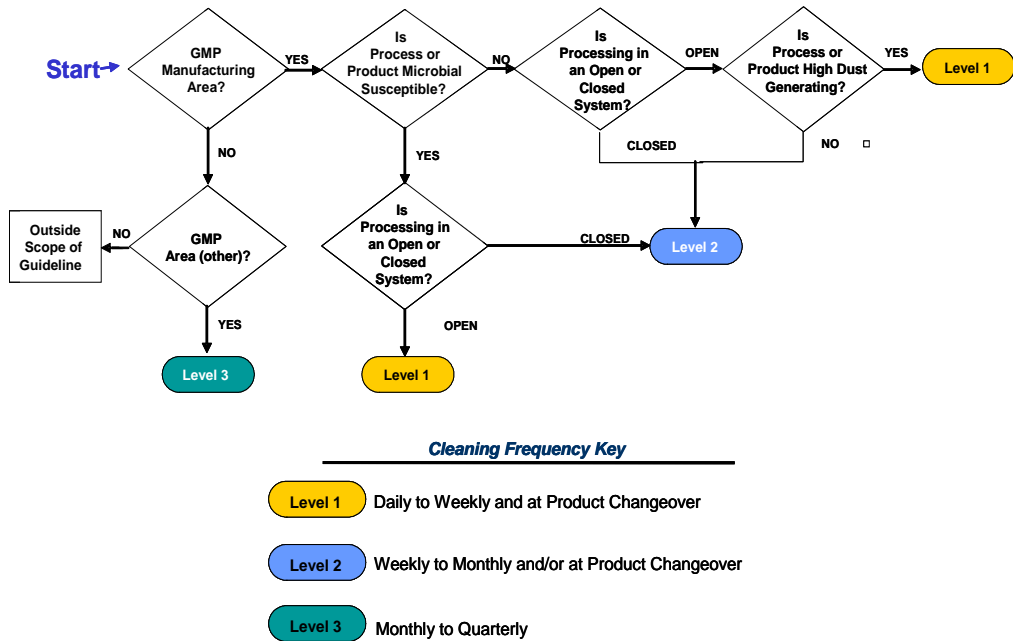
\* No minimum cleaning requirements, other than to inspect and address cleaning needs as appropriate, per cleaning principles.

After development of the prioritization table, a qualitative analysis was performed, based on the product risk prioritization (i.e., product categories) and the process and facility design controls. Subject matter experts were consulted to develop the following decision tree (Table 2) to determine minimum frequency, for areas identified as "green" (i.e. requires a minimum cleaning frequency) in the above prioritization table.

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The decision tree is used by local department heads to define the minimum frequency for cleaning, based on the specific risks associated within their respective operations.

**Table 2 Decision Tree**



**Risk Control**

In the current case study, risk is reduced through the introduction of a structured and standardized approach to determine minimum facility cleaning requirements. The frequency is predicated upon good scientific principles and an understanding of the facility design, process characteristics (e.g. historical dust generating capabilities) and product susceptibility (e.g. inherent microbial inhibition, water content, etc.).

Risk is further mitigated by routine facility audits to ensure that cleaning choices and frequencies are sufficient in maintaining facilities in a GMP compliant state.

**Risk Documentation and Communication**

The risk analysis was reviewed by a senior level quality standards committee to gain alignment on operating principles, risk analysis and risk controls. The resulting tools of the analysis (i.e., Prioritization Table and Decision Tree) are codified in a company quality guidance document. The quality guidance is used to establish local standard operating procedures for execution at the shop floor level. Training is performed against the operating procedure and training records are periodically audited for compliance.

**Risk Review**

As part of the firm's standard practice for the ongoing maintenance of quality guidances, the subject risk analysis (defined as part of the company guideline on facility cleaning) is reviewed by subject matter experts on a periodic basis to ensure that the assumptions and decisions remain valid and justified.