(Cross-)Contamination Control through Effective Equipment Cleaning

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Drug discovery and the scale-up of newly developed manufacturing processes represent an exciting and dynamic field for academic scientists, startups, and small to large pharmaceutical companies. The scale-up to clinical batch sizes, in particular, poses challenges as lab-scale manufacturing expands to batch sizes in the multi-kg range, requiring further optimization of manufacturing processes. Due to the limited and often unknown safety profiles of new compounds, this scale-up is conducted in specialized facilities equipped with adequate contingency measures.

To ensure patient safety, a key issue in the manufacture of active pharmaceutical ingredients (APIs) in multi-purpose, multi-product manufacturing equipment is the adequate management of potential (cross-)contamination, especially when the product portfolio includes both developmental and commercial manufacturing processes.

According to ISPE[1], four major sources can contribute to (cross-)contamination in a multi-purpose, multi-product plant:

1. **Mix-up:** Caused by facility design, labeling, and line clearance.
2. **Retention of Unacceptable Amounts of Previous Products:** Due to insufficient cleaning, cleaning verification, or cleaning validation.
3. **Mechanical Transfer of Contaminants:** Caused by personnel, rodents, insects, gowning, and facility design.
4. **Airborne Transfer:** Resulting from equipment design and/or HVAC systems.

In this whitepaper, we will briefly address the mitigations implemented by Ardena to prevent (cross-)contamination from sources 1, 3, and 4. Mitigations and procedures to prevent (cross-)contamination from source 2 will be discussed in greater depth.

Source 1: Mix-up

To prevent mix-ups, effective line-clearance and correct labeling are essential. Facility design also plays a role, particularly when storage space is inadequate or when the flow of materials and products is not clearly described and adhered to. At Ardena, our facility design ensures adequate storage spaces for both materials and products. Proper use of materials and products is maintained via QR scanning to check the status of materials (e.g., GMP released). Furthermore, practices for material and equipment flow, line clearance, and labeling are clearly documented in procedures and batch records, rendering the risk of mix-up negligible.

Source 2: Cleaning

Cleaning validation for APIs is defined by the FDA[2,3], EudraLex[4], and the ICH[5]. In all these guidelines, equipment cleaning is a critical component of current Good Manufacturing Practice (GMP) requirements. Adequate cleaning procedures are essential to avoid (cross-)contamination of products in a multi-purpose, multi-product facility.

Therefore, it is crucial for a multi-purpose production facility involved in the development and manufacture of APIs and bulk Drug Products (bDPs) to have a scientifically based and organizationally robust cleaning validation concept and equipment cleaning practices.

A cleaning validation program should provide an integrated and systematic approach that considers, among other factors, equipment qualification and equipment cleanability. The program involves testing for acceptable residues on equipment used in pharmaceutical manufacturing. Cleaning validation includes identifying residues, selecting solvents for residue removal, choosing methods for residue detection, selecting sampling methods, setting residue acceptance criteria, conducting analytical method validation and recovery studies, writing procedures, and training operators.

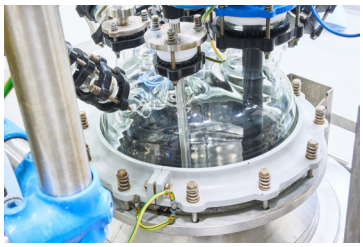
For products under development, cleaning parameters are selected based on available information (e.g., solubility in certain (organic) solvents) and experience with similar compounds/processes within the organization. Therefore, the results of these cleanings are always verified by sampling with a valid analytical method, and equipment is released based on the sampling results. When validating the production process at the end of product development, the effectiveness of the cleaning process should also be validated.

Until recently, our equipment cleaning policy prescribed cleaning of process equipment to a level of <10 ppm to eliminate the risk of cross-contamination. This criterion was used as a default for all product changeovers. The cleaning was not based on Health-Based Occupational Exposure (HBOEL) data such as ADE/PDE. Fully in line with current regulatory guidance[11], we have introduced an improved equipment cleaning program and cleaning validation at Ardena Oss. In the new cleaning practice, the criterion for Maximally-Allowed Carry-Over (MACO) is no longer a default 10 ppm but is calculated based on HBOEL data. The practice consists of a systematic cleaning approach[1-6] and involves testing to verify acceptable residues after cleaning equipment used in manufacturing, regardless of whether the process is validated or still in development, to maintain uniform cleaning execution.

First, acceptable residue limits after cleaning per piece of equipment were determined based on MACO calculations using HBOEL data of the API and expected process yields per piece of equipment[7,8].

The next step in the systematic cleaning approach was to qualify all major equipment (e.g., chemical reactors, product filters, and dosing tanks) and major cleaning systems (e.g., Cleaning-in-Place (CIP) units, washing machines, and hose and appendages rinsing machines) for cleanability/wettability using a fluorescent dye test (Riboflavin) and cleaning with water equivalent to 20% of reactor volume[1,6]. Such a cleanability test with a fluorescent dye allows for the identification of hard-to-clean areas in the equipment.

Based on cleanability studies, dedicated cleaning batch records have been



drafted for different elements of the equipment train (e.g., chemical reactors, dosing tanks, and product filters). The post-manufacturing equipment cleaning concept consists of:

1. **Pre-treatment Cleaning:** Performed in the equipment configuration (train). Pre-treatment cleaning bridges the gap between processing and post-manufacturing cleaning.
2. **Post-manufacturing Cleaning:** Conducted on individual main pieces of equipment based on equipment-specific cleaning batch records. Post-manufacturing cleaning of a reactor involves a CIP process with a once-through rinse with solvent, followed by a boil-out under reflux conditions. For other equipment, Cleaning-Out-Place is designed.
3. **Monitoring of Cleaning Results:** Monitoring is carried out with a predefined rinse using a predetermined volume of monitoring solvent to take a representative cleaning sample from the equipment.

Subsequently, these newly designed cleaning concepts have been validated with a worst-case model process/compound to test the robustness of the concepts in meeting the predefined residue limits per piece of equipment. This approach ensures that when the residue assessment of developmental processes is performed, and the cleaning solvents chosen comply with the solubility requirements for proper cleaning agents, there is a high likelihood of cleaning results being in compliance with the residue limits determined for each piece of equipment.

For each product changeover, the cleaning results are compared with the MACO of the topical changeover. The MACO is based on the Acceptable Daily Exposure (ADE) of the previous compound, the minimal batch size (MBS) of the next compound, and the highest therapeutic daily dose (TDD) of the next compound. Proactively determining the level of cleaning required for a safe changeover enables efficient production scheduling and quick process changeovers for all processes.

Additionally, final cleaning validation, when a process is fully developed, will be much easier and have a high success rate. If a new process does not fit with the pharmacological/toxicological activity profile (i.e., the solubility of the new compound is worse than the solubility of the worst-case compound used in the cleaning validation) of the other products using the same equipment, it will not be introduced unless the equipment can be dedicated to the new process (meaning no other products will be produced in that equipment anymore) [8-10].

Source 3: Mechanical Transfer

Mechanical transfer is prevented by conducting all processes in closed systems. Leak testing of process equipment is performed before the start of any manufacturing step to ensure that no leaking into or out of the process equipment can occur. Materials are stored in closed containers, preferably in their original packaging. Clean equipment is stored and transported with a protective cover to prevent contamination from dust or other external sources. A pest control regimen is in place and regularly monitored. Personnel are trained to maintain proper behavior in the production environment, with safety and hygiene being standard topics during work meetings. These control measures effectively prevent the mechanical transfer of contaminants to the products being produced.

Source 4: Airborne Transfer

The likelihood of airborne transfer of contaminants is low in controlled API and bDP suites, as the product is mostly present in solution in closed production equipment setups. When open handling of chemicals (e.g., NaCl or NaHCO3) is necessary, a point extraction system is placed over the open port. Open handling of active substances (e.g., intermediates or APIs) is conducted in a controlled environment room or a laminar flow booth. Additionally, the HVAC systems in the production environment do not recirculate air without filtering. These control measures minimize the chance of airborne contaminants reaching the product.

Conclusion

The (cross-)contamination prevention measures at Ardena Oss, as well as the equipment cleaning program and cleaning validation approach, are state-of-the-art. This facilitates the rapid introduction of processes still under development into the production facility without compromising the safety of other ongoing production processes in the multi-purpose, multi-product plant. With the new cleaning system, Ardena can achieve speed and flexibility, positioning our clients to meet the challenging timelines often faced during drug development. If a new process is incompatible with existing operations, it will only be introduced if the equipment can be dedicated exclusively to the new process.

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