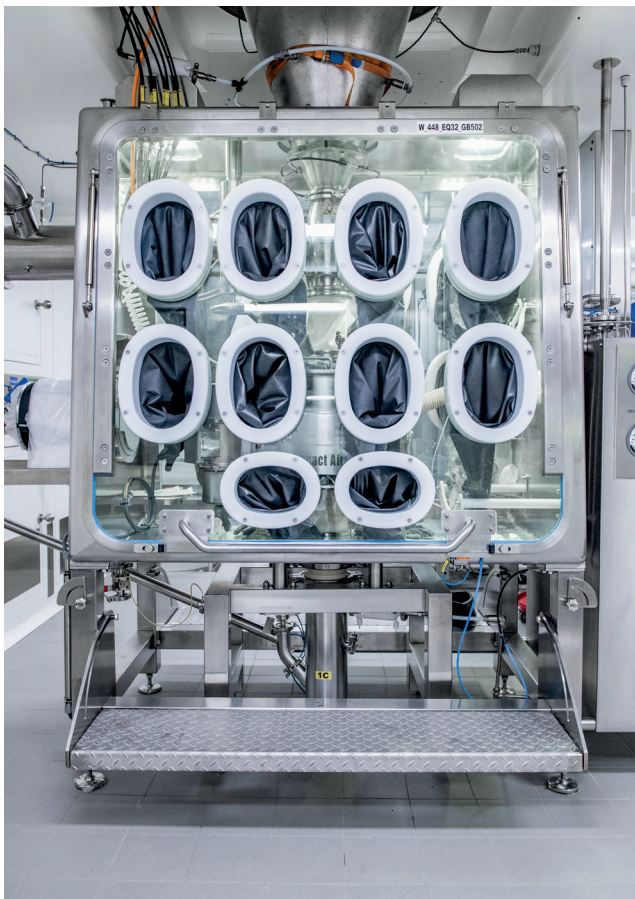




CONTAINMENT EXCELLENCE IN HPAPI MANUFACTURING: A LIFECYCLE APPROACH

By Jan-Klaas Blomme

Source: Ajinomoto Bio-Pharma Services



Containment excellence in HPAPI manufacturing: a lifecycle approach

High potency active pharmaceutical ingredients (HPAPI's) represent a significant part of the drug development pipeline, driven by their high target specificity and ability to deliver clinical efficacy at very low therapeutic doses. This elevated potency is intrinsically associated with stringent toxicological thresholds, frequently resulting in occupational exposure limits (OELs) in the low microgram-per-cubic-meter range or below. Consequently, the risk profile extends beyond operator exposure alone as even trace residues can represent a critical cross-contamination hazard that may compromise product quality and ultimately patient safety. In this context, conventional handling approaches are no longer sufficient for these compounds.

HPAPI manufacturing at an experienced CDMO such as Ajinomoto Bio-Pharma Services therefore requires a robust and fully integrated containment strategy to protect both personnel, product quality and patient safety across all operational phases and throughout the entire product lifecycle. Safe and compliant HPAPI manufacturing is thereby not treated as a discrete asset or isolated capability, but as an integrated system that aligns safety, quality, and operational performance from early development through commercial supply. This approach goes beyond incremental upgrades of personal protective equipment (PPE) and is founded on a comprehensive containment strategy combining engineered controls with robust operational and organizational measures to ensure sustainable containment performance.

From toxicological assessment to a robust HPAPI containment strategy

At Ajinomoto Bio-Pharma Services occupational exposure banding (OEB) is applied as a systematic approach to categorize substances into defined exposure bands based on their potential health hazards. OEB classification supports consistent selection and implementation of a standardized containment strategy, particularly when a compound-specific OEL has not yet been established.

At the project initiation each active pharmaceutical ingredient (API) and relevant intermediates undergo a comprehensive in-house toxicological assessment. The resulting data are used to assign the appropriate OEB with a corresponding containment performance target (CPT) and to derive specific health-based exposure limits (e.g. MACO).

These scientifically derived parameters provide the basis for design and implementation of the appropriate engineering and operational controls. As a result, high potency product handling is governed by robust, well-defined workflows in which engineered containment forms the primary layer of the containment strategy, while operational controls ensure consistent and compliant execution. Together, these measures protect personnel, product quality and ultimately the patient across all stages of the product lifecycle, from development to commercial manufacturing.

From a CDMO perspective, this approach supports an accelerated project execution and high manufacturing reliability by embedding a scientifically grounded and risk-based containment strategy from early in the project, thereby reducing late-stage redesign, deviations and avoidable operational constraints.



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The basis of our containment strategy

At Ajinomoto Bio-Pharma Services the hierarchy of controls is applied by prioritizing engineering controls over operational measures to achieve effective and reliable exposure mitigation. Engineering controls aim to reduce or eliminate exposure by implementation of advanced containment technologies, robust equipment design and an appropriate facility layout.

Supported by extensive expertise in the design and application of engineered containment solutions, an in-house engineering team works in close collaboration with the operational team to integrate containment considerations from the earliest design stages. This ensures alignment between process requirements, equipment capabilities and containment performance expectations. In addition, closed process design is treated as a fundamental engineering control within the containment strategy as it minimizes exposure potential at the source. This approach is systematically embedded by a highly proficient and innovative R&D process development team which results in scalable manufacturing processes for HPAPI's across all development phases.



Operational controls rely on standardized procedures and protocols for handling high-potency compounds, supported by trained personnel to ensure the safe and consistent execution of activities within these engineered systems. PPE is applied as a supplemental layer to address residual risk and is not relied upon as the primary means of protection.

As an experienced HPAPI manufacturer, Ajinomoto Bio-Pharma Services does not consider containment as a production-floor safeguard alone, but an end-to-end control strategy spanning the full manufacturing lifecycle. This extends beyond chemical synthesis and final isolation to all supporting activities, including warehousing (sampling and dispensing), process development, quality control laboratories, maintenance and waste handling. Each representing potential exposure scenarios to potent compounds, intermediates, residues or contaminated surfaces.

Containment at the source and closed processing as the default

As a default and wherever technically feasible, containment is applied at the emission source through engineered systems. Primary containment provides the most effective and reliable means of exposure control by physically isolating personnel from the product, thereby reducing reliance on operational controls and PPE.

Primary containment used at Ajinomoto Bio-Pharma Services includes closed sampling and dispensing systems, high-containment isolators and barrier technologies, closed material transfer systems, contained discharge technologies, equipment-integrated containment solutions and contained analytical sample preparation. Central to the effectiveness of these systems is robust interface and connection design, ensuring a leak-tight integration between equipment components.

During the selection and design of primary containment systems, cleanability and decontamination requirements are treated as integral criteria to ensure safe and sustainable operation. Primary containment solutions should be compatible with cleaning strategies such as cleaning-in-place (CIP) to enable effective removal of high-potency residues while minimizing system breach and manual intervention.

In addition to engineered containment technologies, process design represents a fundamental form of primary containment. By embedding containment principles directly into the process, exposure risks can be minimized or eliminated. This is achieved through strategies such as the in-situ operations (e.g., in-situ drying, sampling or cleaning), Process Analytical Technology (PAT) for in-line process monitoring and the use of telescoping to maintain closed transfer between process steps. Importantly, these design principles should be incorporated from the early process development through scale-up into commercial manufacturing to ensure consistency, scalability and robustness of the containment approach across the entire product lifecycle.



Facility-integrated secondary containment controls

Even when robust primary containment is implemented, a residual risk of exposure remains. To address this residual risk, secondary containment is implemented as a facility-level engineering control within the overall containment strategy at Ajinomoto Bio-Pharma Services.

Secondary containment limits the spread and impact of high-potency compounds in the event of an unintended release. Thereby extending exposure control from the source to the surrounding environment and providing a critical additional layer for protection of personnel and product. The required level of secondary containment is defined through a risk-based approach that considers the assigned OEB, the quantity of material handled, the primary containment used and the nature of the activity performed.

The secondary containment used is achieved through a combination of local exhaust ventilation (LEV), HVAC-based segregation, pressure cascades, HEPA filtration and controlled airflows that establish a directional air flow from clean to potentially contaminated areas. High-potency operations are conducted within dedicated HPAPI areas that are physically separated from other activities. Airlocks with defined material and personnel flows are implemented to maintain spatial and functional separation and to support the defined gowning procedures.

During facility design several key considerations are integrated to ensure sustained secondary containment performance. This includes provisions for effective cleanability as well as enabling maintenance activities to be executed under contained conditions. In parallel, the design incorporates preventive maintenance and continuous monitoring of critical parameters such as airflow directionality and pressure differentials to ensure containment systems remain within their qualified state during routine operation.

Operational controls as a critical element of our containment strategy

Tertiary containment comprises the combination of operational and organizational measures such as clearly defined procedures, training, controlled access and the appropriate use of task-specific PPE. In alignment with the hierarchy of controls, these measures are applied as a complementary layer to primary and secondary containment.

Despite engineered controls, loss of containment is frequently linked to human factors, particularly during atypical manipulations or deviations from predefined methods. Ajinomoto Bio-Pharma Services therefore emphasizes not only the presence of containment, but its consistent and correct use. This requires a workforce that understands not only how to execute tasks, but why containment is essential for protecting both operators and patients.



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Human Factors in Containment: **Training, Gowning and Incident Management**

To support consistent and reliable containment performance, a comprehensive training program is implemented with equal emphasis on technical proficiency and containment behaviour. Personnel are trained in the correct execution of process operations and in the fundamental principles governing containment and exposure control. The training approach incorporates thorough training of the applicable procedures and hands-on simulations that replicate high risk tasks, allowing personnel to demonstrate competence in critical interventions under controlled conditions before performing them in a GMP manufacturing environment. This program is not limited to solely manufacturing personnel but extends to all relevant operational functions, such as maintenance activities, recognizing that containment integrity depends on consistent practices across all activities involving product contact or system intervention.

During training, particular attention is given to gowning and de-gowning procedures required for high potency operations. All personnel follow a defined and validated gowning sequence prior to entering HPAPI areas, with requirements tailored to task-specific risk and containment status.

In addition, structured and thoroughly trained procedures are in place to address accidental spills, loss-of-containment events and other emergency situations. In the event primary containment is compromised, the affected area is subjected to a defined decontamination and verification process. Release for further operations is permitted only after visual and analytical confirmation demonstrates that predefined cleanliness and exposure-control criteria have been met.

Embedding cleaning and change-over **in the containment strategy**

As a multi-product CDMO, cleaning and changeover operations are a critical part within the containment strategy, recognizing that the exposure and cross-contamination risk can increase during equipment opening, disassembly or manual access. These activities are therefore designed and executed under controlled conditions to maintain containment integrity as much as possible throughout the cleaning lifecycle.

Following each production campaign, equipment is cleaned in accordance with validated and scientifically justified compound-specific cleaning procedures. Cleaning effectiveness is not assumed but continuously verified through validated analytical methods. The outcome of this analytical verification is systematically evaluated to support changeover decisions, including the assessment of actual carry-over versus a scientifically derived Maximum Allowable Carryover (MACO). This ensures that both operator safety, product quality and patient safety are maintained when transitioning between products.

In addition, manufacturing areas are released for subsequent operations only after formal line-clearance procedures have been completed. These include analytical verifications (e.g. swab sampling of surfaces) to confirm residual contamination levels are within predefined acceptance criteria and that exposure and cross-contamination risks are effectively controlled to protect the personnel.

Safety culture as an enabler of operational control

As an experienced CDMO for small molecules and peptide, with long lasting leading position in hazardous chemistry Ajinomoto Bio-Pharma Services reinforces operational controls through a strong culture of safety and learning. Incident and near-miss reporting is actively encouraged, enabling timely corrective and preventive actions and supporting organizational learning through trend analysis. Regular task risk assessments are performed and refreshed to reflect operational experience, resulting in continuous improvement of procedures, work instructions and training content. This closed-loop approach helps ensure operational controls remain current, practical and effective as processes and products evolve.

Personal Protective Equipment (PPE): Task-Specific and Always the Final Layer

PPE requirements are defined through a structured, task-specific assessment considering the assigned OEB, the nature of the activity, the effectiveness of primary and secondary containment and potential non-routine scenarios such as maintenance or upset conditions. This approach ensures consistent, risk-based application of PPE while supporting reliable operator protection.



AJINOMOTO BIO-PHARMA SERVICES REINFORCES OPERATIONAL CONTROLS THROUGH A STRONG CULTURE OF SAFETY AND LEARNING.



| Verified performance through testing

As an experienced CDMO in HPAPI manufacturing Ajinomoto Bio-Pharma Services recognizes that engineered containment solutions alone do not guarantee effective exposure control. The effectiveness of a containment strategy is determined by its ability to achieve the required performance under representative operational conditions. Containment performance is therefore verified using the standardized SMEPAC methodology, enabling quantitative evaluation of airborne particulate emissions and surface contamination against predefined containment performance targets. The resulting data provide an objective basis to confirm that containment systems and associated operating practices perform as intended under realistic process conditions.

Containment performance is systematically verified for each new containment strategy as an integral component of the qualification process and is re-evaluated following significant modification to ensure continued compliance with predefined performance targets. At Ajinomoto Bio-Pharma Services The SMEPAC-based performance verification is conducted in-house under the oversight of the EHS department. Testing is performed under actual process conditions and executed by trained operational personnel to generate representative results. In this way, containment performance verification extends beyond individual equipment qualification and includes the full process context, including operator interactions. In alignment with a lifecycle approach, cleaning and changeover activities are explicitly included within the scope of performance verification.

The outcomes of these evaluations provide an objective basis for the continuous optimization of engineering and procedural controls. In accordance with the hierarchy of controls, the effectiveness of the containment strategy is evaluated independently of PPE, which remains a supplementary measure for the mitigation of residual risk.

Ongoing assurance of worker protection is further supported through a structured occupational health surveillance program, including periodic medical evaluations. This additional layer of verification helps confirm that the integrated containment strategy continues to perform as intended, ensuring sustained protection of personnel over time.



**ENGINEERED CONTAINMENT
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