

From OEL to Commercial Supply: Designing Robust High-Potency Oral Solid Manufacturing

Highly potent APIs are becoming more significant across the pharmaceutical development pipeline. Market estimates vary, but the direction is consistent: the global HPAPI market hit around USD 29.87 billion in 2025 and forecasts growth to USD 48.29 billion by 2033^[RG1.1], driven by demand for targeted medicines, oncology therapies and other potent molecules.¹

For oral drug products, however, the challenge is not simply to handle HPAPI safely. Whether the intended medicine is a tablet, capsule, or liquid formulation, success depends on integrating toxicology, formulation science, process engineering, containment and lifecycle planning from the outset.

An isolator, negative-pressure suite or stated occupational exposure band (OEB) may be an important part of the answer. None, in isolation, demonstrates that a product can be manufactured safely, reproducibly and at commercial scale. The more meaningful test is whether the proposed operating model protects people, prevents cross-contamination, preserves critical quality attributes and remains practical through development, technology transfer and routine supply.

Starting With Exposure

Containment discussions often begin with an OEB designation, such as OEB 4 or OEB 5. Although useful as an operational shorthand, OEBs are not universally harmonised across the industry and should not replace compound-specific assessment.

The starting point is the occupational exposure limit, or OEL: the average airborne concentration of an API considered acceptable over a defined period, commonly an eight-hour time-weighted average. The OEL defines the exposure outcome that a control strategy must achieve. It does not prescribe a particular piece of equipment, room classification or facility layout.

Other toxicological limits also inform manufacturing decisions. Permitted daily exposure (PDE), also known as acceptable

daily exposure (ADE), is relevant to the assessment of product carryover, cross-contamination and cleaning limits in multiproduct facilities. The no-observed-effect level may contribute to defining an acceptable daily exposure where appropriate toxicology data are available.

These distinctions have practical implications. Two products within the same broad OEB may require different containment strategies because they differ in batch size, particle characteristics, powder flow, dose, route of administration, process route and handling requirements. A fine, cohesive and electrostatically charged powder handled through multiple open transfers presents a different risk profile from a material processed through closed charging and transfer systems.

A robust new-product-introduction process should therefore assess the molecule before it reaches the manufacturing floor. The review should bring together toxicology, pharmacology, OEL and PDE data, proposed batch size, formulation route, equipment requirements and operational tasks. A risk assessment can then identify where material could be released, where product may be retained, and what controls are required before development or manufacture begins.

Containment as an Operating System

For potent products, containment is often described in terms of equipment or facility

features. This risks missing the broader point: containment is the demonstrated performance of the complete operating system.

Exposure and cross-contamination risks should be assessed across four principal pathways:

- Airborne transfer of dust or aerosol.
- Mechanical transfer through equipment, materials or movement between areas.
- Personnel transfer, including garments, gloves and movement patterns.
- Product retention on contact surfaces, seals, components or difficult-to-clean locations.

The highest risks frequently occur at interfaces between operations. Material receipt, dispensing, charging, transfer, sampling, discharge, cleaning, maintenance and waste handling can all create exposure opportunities, even when the principal unit operation is enclosed.

Primary containment should be positioned as close as possible to the material source. Suitable equipment operates under negative pressure and is designed to prevent release during normal processing. Secondary containment is then provided by the surrounding facility, including air-management systems, pressure cascades, airlocks, access controls, cleaning and decontamination areas, and appropriate filtration.





granule-size distribution, fines and final tabletability. Development must therefore establish conditions that produce not simply acceptable granules, but a consistent final dosage form with the required hardness, friability, disintegration, dissolution and content uniformity.

The risk profile for oral liquids is different. They can improve administration and dosing flexibility, but may be more vulnerable to degradation and microbial growth, increasing demands on formulation design, preservation, packaging compatibility and dose accuracy. With potent APIs, the greatest containment risk is often at charging and wetting: once the material is fully wetted, airborne exposure potential is substantially reduced.

Fine powders can disperse during transfer, and static charge may intensify dusting. Poorly controlled liquid addition can cause splashing or aerosolisation, while particle size, hydrophobicity and wettability can delay dispersion or cause clumping. Contained charging and closed processing must therefore be designed alongside order of addition, mixing energy, wetting rate and vehicle selection to achieve safe dispersion without compromising product quality or manufacturability.

Building Containment into QbD

Quality by Design provides a useful structure for integrating these decisions. It begins with the quality target product profile and identifies the critical quality attributes that the finished medicine must achieve. Development work then determines the critical process parameters that affect those attributes and establishes a proportionate control strategy.

This layered model is more robust than relying on a negative-pressure room alone. It also provides a framework for evaluating what happens if containment is breached. Air handling, dust collection, room segregation and safe material flow are important, but their purpose is to support the primary barrier, not to substitute for it.

The strategy must account for normal and abnormal operations. It is not enough to assess a process while equipment runs as intended. Teams should consider foreseeable interventions: material charging, sampling, container changes, clearing a blockage, responding to alarms, replacing components, cleaning and maintenance. A process that is technically enclosed but routinely requires manual intervention may introduce operational weakness.

PPE remains important for work within a controlled environment and for response to a system failure. It should not, however, be treated as the primary containment barrier during normal operations. Where potency demands a high level of control, engineering and process design must do the bulk of the protective work.

Oral Formulation Changes the Risk Profile

For oral products, formulation choice determines where and how containment must perform. The aim is not only to prevent material release, but to do so while maintaining the critical quality attributes of the finished medicine.

For solid oral dosage forms, key risk points include dispensing, blending, milling, granulation, compression or encapsulation, sampling and cleaning. Fine powders can become airborne during charging and discharge, while particle size, electrostatic

charge, cohesiveness and flowability influence dusting, segregation and material hold-up. For low-dose products, containment must also protect blend uniformity and avoid transfer steps that increase segregation risk.

Roller compaction illustrates the connection between formulation, process design and containment. In this dry-granulation route, a powder blend is compacted between counter-rotating rollers into a ribbon, then milled into granules for tableting, encapsulation or sachet filling. It can be valuable where direct compression is unsuitable and wet granulation creates stability concerns, particularly for moisture-sensitive, heat-sensitive or poorly flowing materials. Its integration with contained feeding, sealed transfer and milling can also reduce open powder handling.

However, enclosure alone does not make the process robust. Compaction force, roller gap and speed, feed rate and milling conditions affect ribbon density,



For a high-potency programme, containment must sit within this framework. Early formulation and process studies should identify not only whether a product is technically feasible, but also where dust may be generated, what material-handling steps are required, where manual intervention may occur, how samples can be obtained and how equipment can be cleaned.

This approach can reduce the risk of developing a process that performs well in a laboratory but cannot be transferred safely or efficiently into a contained manufacturing environment.

Process analytical technology can help where inline or real-time information reduces the need to open equipment. Automation and programmable adjustments can also reduce manual intervention, provided the process is well understood and teams can manage deviations. The technology alone is not the strategy. Its value lies in delivering relevant process information and enabling timely control of conditions that affect both product quality and containment performance.

For roller compaction, structured design-of-experiments work can define how compaction force, roller gap, roller speed and feed conditions affect ribbon properties, granule attributes and final-tablet performance. This creates a stronger basis for establishing a design space and identifying the parameters that must remain under control as a process moves towards larger-scale manufacture.

Designing for Transfer and Commercial Supply

A development batch conducted safely does not prove that a process is commercially sustainable. Scale-up may change material quantities, feed behaviour, dust load, transfer routes, cleaning burden and the practical nature of interventions.

Containment therefore needs to be addressed explicitly during technology transfer. The transfer package should cover more than formulation composition, manufacturing instructions and analytical methods. It should capture material flow, equipment interfaces, containment-critical steps, sampling requirements, cleaning rationale, waste handling and anticipated deviations.

A gap analysis is valuable before transfer begins. Differences in equipment geometry, feeder design, vessel size, transfer routes and cleaning access can alter powder behaviour



and exposure potential. Identifying these differences early makes it possible to determine whether process parameters, equipment arrangements or operating procedures need to change before batches are executed at the receiving site.

Cleaning is particularly important in multiproduct facilities. Potent materials may remain on product-contact surfaces, seals, transfer assemblies or inaccessible areas of equipment. A sound cleaning strategy begins during new-product assessment and is informed by toxicology, product characteristics, equipment design and the risk of carryover to the next product.

Appropriate swab and rinse sampling methods, cleaning verification and lifecycle validation provide the evidence that the strategy remains effective. The aim is not necessarily to require a dedicated facility for every potent product. It is to establish whether the facility, equipment train, cleaning programme and operating procedures can provide an appropriate, demonstrable level of control.

Questions That Matter

A stated OEB capability is only a starting point for sponsor due diligence. The questions that determine whether a manufacturing strategy is truly robust are more specific:

- Has the compound been assessed using appropriate toxicological and pharmacological information before site acceptance?
- How will the OEL be translated into controls across dispensing, transfer, processing, sampling, cleaning and waste?

- Does the process protect both operator safety and the product's critical quality attributes?
- How are routine and non-routine interventions managed?
- What evidence supports containment performance at the intended scale and for comparable operations?
- How will containment-critical knowledge transfer from development into clinical and commercial manufacturing?
- How are cleaning, carryover and multi-product risk managed over the product lifecycle?

High-potency oral manufacturing is not defined by an OEB label, a facility claim or one item of containment equipment. It is defined by the ability to translate toxicological requirements into a repeatable manufacturing system: one that protects operators, preserves product quality and remains viable from the first development batch through commercial supply.

REFERENCES

1. High Potency Active Pharmaceutical Ingredients Market (2026 – 2033) <https://www.grandviewresearch.com/industry-analysis/high-potency-active-pharmaceutical-ingredients-hpapi-market>



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