Enabling Oral Delivery of TPDs:
The CDMO Path to Oncology's Next Frontier

No major scientific breakthrough comes without its challenges. This is certainly true of targeted protein degraders (TPDs), which have rapidly become one of the most dynamic areas within oral solid dose drug development.

The idea behind TPDs, encompassing both proteolysis-targeting chimeras (PROTACs) and molecular glues, emerged in the early 2000s as a novel means of removing, rather than merely inhibiting, disease-causing proteins. The first PROTACs, described in 2001 by the Crews and Deshaies laboratories, used peptide linkers to connect a target ligand with an E3 ubiquitin ligase ligand, ultimately directing the target protein for degradation. While conceptually elegant, these early molecules were large, unstable and lacked permeability, making them unsuitable as therapies. Molecular glues had a precedent in drugs such as thalidomide, but their discovery was largely serendipitous and their mechanisms poorly defined.

For years, TPD research remained largely confined to academic settings, constrained by limited availability of E3 ligases, the absence of predictive models for ternary complex formation, synthetic difficulties and the prevailing view that molecules of such size could never be orally bioavailable. Over the last decade, however, advances in structural biology, computational modelling, small-molecule chemistry and clinical validation have shifted this perspective. The central challenge is no longer whether TPDs can function, but how to deliver these inherently bulky and poorly soluble molecules in a form that the body can effectively absorb.

The CDMO Advantage

TPD molecules are frequently described as "brick dust" compounds because of their large and complex structures, which translate into poor solubility in the gastrointestinal tract. Even when dissolution is achieved, their bulk also restricts permeability across intestinal membranes, meaning only a fraction of the administered dose reaches systemic circulation. The consequence is low bioavailability in patients, a frustrating paradox in which highly potent therapies for serious, often life-threatening diseases such as cancer face fundamental delivery hurdles.

In parallel, the past two decades have brought significant progress in the capabilities of contract development and manufacturing organisations (CDMOs), particularly in formulation and process science. The most established CDMOs have supported the development and manufacture of hundreds, if not thousands, of molecules over this period, building deep institutional knowledge of best practices in process development and large-scale manufacturing. Those with experience in handling highly potent compounds at occupational exposure band 5 (OEB5, ~10 ng/m^3) bring an added advantage: the ability to manage challenging molecules safely and effectively. While TPDs are not always categorised as highly potent, the expertise and infrastructure developed for OEB5 compounds provide a strong foundation for managing their complexity.

That said, even among larger CDMOs, not every organisation possesses the full suite of in-house capabilities needed to enhance the bioavailability of complex modalities. Advanced enabling technologies such as spray drying, hot-melt extrusion and nanomilling demand specialist expertise and dedicated facilities. The leading providers in this area are typically those focused on these cutting-edge platforms. Encouragingly, an emerging model within the pharmaceutical supply chain is addressing this gap, the rise of strategic partnerships designed to align CDMOs, technology specialists and drug developers in pursuit of optimal solutions.

Oncology is the industry's growth engine and the proving ground for oral targeted modalities. Estimates vary by methodology, but most place the global oncology market at ~$225–$356 billion in 2024–2025, with forecasts clustering around $600–$900 billion by 2034 (≈11% CAGR).[1,2,3] At the same time, small molecules still dominate US approvals. In 2024, 64% of CDER's novel approvals were small molecules, broadly consistent with recent years, and the majority of these are administered orally. Industry summaries indicate that ~60% of FDA NME approvals are small molecules and ~80–90% of those are oral, underscoring the continued centrality of OSD in oncology pipelines.

Potency and complexity further raise the bar on development and manufacturing. Multiple analyses suggest ~45% of recent small-molecule NCEs qualify as highly potent (HPAPI),[4,5] demanding OEB-4/5 controls and specialist containment and handling. For TPDs, this landscape is even more acute; market studies project rapid category growth as programmes mature, with published CAGRs ranging from ~21% to ~35% through 2035.[6,7]

Put together, oncology's scale, the predominance of oral small molecules and the rise of HPAPIs make CDMOs with deep potency, formulation and tech-transfer expertise indispensable, particularly when moving TPDs from concept to robust, scalable OSD products at speed.

Strategic Partnerships

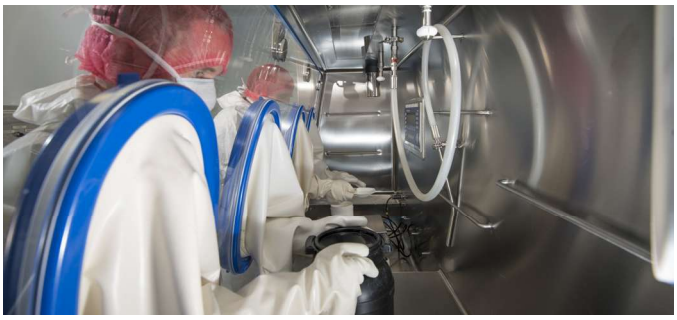
Introducing new technologies into a CDMO environment can be a lengthy, resource-intensive and costly endeavour, particularly when bridging technical skills gaps. This naturally raises a question: why not leverage complementary expertise across the industry and connect them within a collaborative network that spans the pharmaceutical supply chain?

Such an approach allows CDMOs to focus on their core strengths (such as process development, technology transfer,

scalable manufacturing, clinical and commercial packaging, and essential support functions like regulatory and analytical services) while simultaneously tapping into best-in-class enabling formulation technologies. The result is access to cutting-edge capability without the risks of protracted timelines or costly integration efforts. Yet forming partnerships is only the starting point; it is effective partnership management that ultimately determines whether a therapy reaches the clinic and patients in the fastest, most efficient and most cost-effective way possible.

Traditionally, a drug sponsor would present its substance to a CDMO, only to discover that an enabling technology was required elsewhere. The sponsor would then have to engage an upstream specialist, whose work was often disconnected from the CDMO that would eventually assume responsibility for the product. This fragmented process created inefficiencies, slowed progress, and most importantly, delayed patient access to critical therapies.

A CDMO's real differentiator lies in its project management expertise, developed over decades of guiding complex molecules through multiproduct facilities and across every stage of the development lifecycle. The solution, therefore, is to establish the CDMO as the project's single point of contact (SPOC). In this role, the CDMO coordinates directly with its strategic partners, aligning on drug substance characteristics, product requirements and the most suitable enabling technologies. Detailed technical exchanges occur within a single, managed framework, ensuring seamless knowledge transfer and preventing costly omissions or delays in downstream development and manufacturing. In oncology, where speed to clinic literally affects patient outcomes, the SPOC model ensures that enabling technologies for oral targeted molecules, such as TPDs, are fully integrated and time-efficient, streamlining transitions from discovery to first-in-human trials.

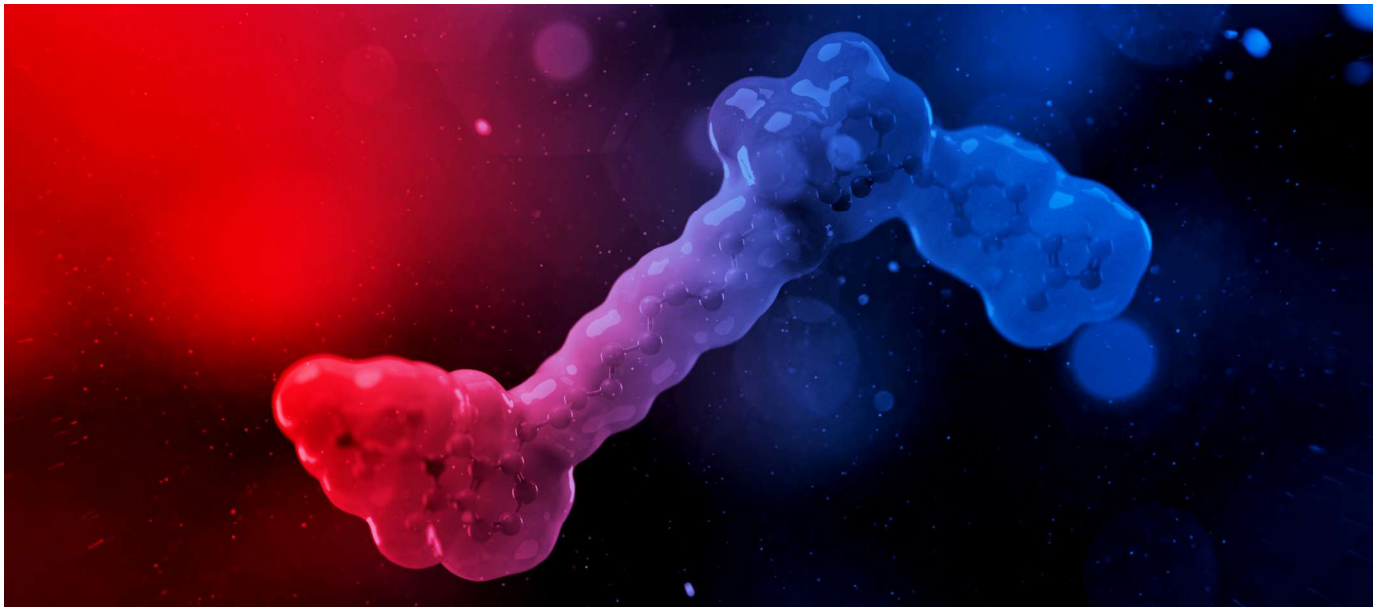


Enabling Technologies

Adopting a platform-agnostic approach ensures that the client's product dictates the choice of technology, rather than forcing a molecule into an ill-suited process. For "brick dust" TPDs in particular, several established enabling technologies have proven effective in enhancing bioavailability.

Spray drying converts TPDs into amorphous solid dispersions by dissolving the drug substance within a polymer matrix at the molecular level. By removing the crystalline structure that typically restricts dissolution, the process yields a high-energy amorphous form that dissolves more readily in gastrointestinal fluids. For TPDs, spray drying can significantly improve the apparent solubility of these large, hydrophobic molecules while offering scalability from early development through to commercial production.

Hot-melt extrusion (HME) achieves intimate molecular-level mixing between TPDs and pharmaceutical polymers without



the use of solvents. Through the application of controlled heat and shear, the drug substance is blended with carrier polymers to form a homogeneous solid solution or dispersion. As a continuous process, HME delivers excellent content uniformity while improving both solubility and permeability by disrupting crystalline structures and establishing more favourable thermodynamic conditions for dissolution.

Nanomilling reduces TPD particles down to the nanometre scale, vastly increasing the surface area available for dissolution. This mechanical size reduction can accelerate dissolution rates by orders of magnitude, in line with well-established dissolution principles. For TPDs, often hindered by both poor solubility and sluggish dissolution kinetics, nanomilling provides a straightforward means of enhancing bioavailability, especially when combined with stabilising surfactants and polymers to maintain long-term stability.

Together, these technologies offer complementary pathways to overcoming the solubility and permeability challenges inherent to TPDs. By applying the right approach, or even a combination of methods, developers can unlock the therapeutic potential of these complex molecules and advance them toward clinical and commercial success.

Looking Ahead

While today's TPDs benefit from proven enabling technologies, one certainty remains: the pharmaceutical landscape will continue to evolve. Cancer biology continues to drive innovation in oral targeted therapies, particularly in addressing "undruggable" targets, protein classes that traditional small molecule inhibitors cannot modulate. TPDs, including PROTACs and molecular glues, offer a compelling route to degrade these proteins, a mechanism that is now increasingly viable as formulation science and CDMO-enabling technologies align.

As formulation data accumulates across the industry, enabling platforms will advance in step, further broadening the toolkit available to drug developers. The shift toward closer collaboration between CDMOs and specialist formulation partners comes at precisely the right moment. With the TPD market projected to expand at a CAGR of roughly 21% through 2035, outpacing even biologics, commercial momentum is now firmly aligned with their therapeutic promise.

For patients awaiting these therapies, such collaboration delivers more than operational efficiency; it creates the essential bridge between laboratory innovation and real-world access to treatments for cancer and other chronic diseases. By uniting deep manufacturing expertise with state-of-the-art formulation and processing technologies, the industry is now positioned to realise the therapeutic vision that has surrounded TPDs for over two decades. In this light, the long-standing "curse" of these complex molecules may at last be giving way to the prospect of meaningful, life-changing therapies.

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