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From Orphan Drugs to Advanced Therapies: Piramal's Global R&D Perspective

How Piramal Pharma is shaping resilient, patient-centric development across OSDs, HPAPIs, and sterile injectables.

As drug pipelines diversify and patient needs become increasingly complex, formulation R&D has taken on a pivotal role in bridging discovery and commercialization. From orphan drug programs requiring rapid, small-batch development to advanced modalities like peptides and oligonucleotides, sponsor companies are seeking CDMO partners who can deliver both speed and scientific depth.

In this Pharma Matters Q&A, *Contract Pharma* speaks with Brad Gold, global formulations R&D head, and Sundar (Sunny) Neelakantan, director of R&D at Piramal Lexington, about how Piramal Pharma Solutions is evolving its global R&D and manufacturing footprint. They discuss the latest advances in high-potency OSDs, controlled-release platforms, sterile injectables, and patient-centric dosage forms, while sharing insights into how Piramal's integrated, multi-site approach is designed to meet regulatory demands and accelerate time-to-market.

Contract Pharma: *Contract Pharma's recent coverage of oral solid dosage (OSD) trends quotes Piramal on the rising demand*

for smaller batch sizes and integrated services. Can you elaborate on how PPS is adapting its formulation R&D and manufacturing strategy to these developments—and what that means for clients with orphan, niche, or orphan-oriented assets?

Brad Gold / Sunny Neelakantan: Catering to the breakthrough and orphan designations, which typically require fast-track dosage form development and regulatory approval, Piramal has established its PPDS (Piramal Pharmaceutical Development Services) site in Ahmedabad, India to provide rapid development and clinical trial material manufacturing for Phase I and II drug programs. In this connection, its ability to handle potent drugs, flexibility in batch sizes from 100 grams to 50 kg, together with process equipment to match, Piramal has established itself as the best choice for drug development. Ultimately, these robust formulations are transferred to an integrated commercial site in the Piramal network, where the niche smaller batch sizes can be manufactured.

CP: *You both have deep experience with high-potency OSDs and containment design. What are the current challenges and breakthrough technologies in safely formulating and manufacturing HPAPIs, particularly in an R&D-to-commercial environment? How does PPS manage scalability and regulatory expectations in that context?*

Brad: Obviously, the challenge here is answering every scale with containment applications around process equipment. A potent drug where the batch size is, for example under 100 kg, with some exceptions, may be formulated using continuous processes that lend themselves to flexibility around batch sizes. For example, dry granulation using roller compaction is a continuous throughput unit operation that also lends itself by design, to containment prior to and after compaction and milling. Sometimes, scaling up in this context simply means running the roller compactor longer, or in the case of unit dose manufacture, running an encapsulator longer. In the case of the latter, picking the right type and size of encapsulator provides for enough in-process sampling to prove process control.

CP: *You hold patents around sustained-release, zero-order and near zero-order release formulations. How are controlled-release platforms evolving today—from early-stage development through commercialization—and what CDMO innovations do you foresee that will benefit clients looking for differentiated delivery?*

Brad: Drugs are being delivered to active sites in the body more efficiently by being conjugated to an antibody that is recognized by specific antigens at the cellular level. Prodrugs have been around for some time, but they continue to show promise in metering drug through the GI tract. During early sustained-release drug development, correlating drug plasma levels with Scintipharma's gamma scintigraphy (i.e. site of absorption) has given drug development scientists a tool for precision delivery. Finally, the advent of micro-tablets to facilitate delivery of multiple mini-doses by weight or age, provide proper dosing regimen for certain therapies.

CP: *With Piramal's history in implementing operational excellence modules, lean, and QbD principles across multi-site R&D (US, UK, India), how do you ensure consistency in formulation quality, knowledge transfer, and risk reduction as molecules move from R&D into scale-up and tech transfer?*

Brad: We employ an integrated and multi-site Stage Gate approach to product development and commercial readiness, one in which the appropriate stakeholder departments for each stage must demonstrate progress toward a deliverable prior to progressing to the next stage. Our R&D and Tech Transfer Leadership Teams ensure that the Stage Gate prerequisites are occurring at each site.

CP: *You both have led the evaluation and implementation of new technology platforms. Can you share examples of R&D or manufacturing technologies you've introduced recently and the impact these have had on accelerating development timelines or improving robustness?*

Brad: Two of our sites have acquired multi-layer tableting technology to better tackle bi- and tri-phasic drug delivery in the same dosage form. Our Morpeth UK site continues to further its tablet in tablet technology, enabling both IR and ER release profiles from the same dosage unit. We recently acquired ASAP stability modeling and use it routinely as a means to get drug prototype stability data faster. At all three of our commercial manufacturing sites, we are able to comply with multiple regulatory bodies that demand 100% automated visual inspection, and the latter is coupled with the last step in manufacturing, making it a continuous manufacturing technology.

CP: *As individuals deeply involved in CMC strategy, what are the most pressing regulatory or documentation challenges you face in formulation development today, and how are you gearing PPS's formulation R&D to meet those evolving expectations early in project timelines?*

Brad: We are predicting nitrosamine chemistry pathways during chemical (API) development and dosage form development, such that clients know whether their API poses a risk (or not) in the overall drug development pathway. To that end, we perform risk assessments at all our sites using a standard template and employment of a risk assessment using Risk Priority Number through an FMEA tool. Just as important, we

can employ full chemical testing at two of our sites across our network.

CP: *Piramal stresses patient centricity and offers flexible dosage forms across OSD, liquids, creams, injectables, and specialized forms. From your vantage points in formulation R&D, how is client demand evolving in terms of patient-centric formats and how are you creating adaptive platforms to address those needs efficiently?*

Brad: Piramal has developed multiple dosage units for the same drug, across several patient populations. For example, we have developed a chewable tablet incorporating taste masking technology in a pediatric, while an adult dosage form uses a standard tablet. We have used a Sprinkle Capsule approach for both geriatric and pediatric populations. We have experience across our network developing minitablets for ease of dosing and flexibility across multiple age groups.

CP: *PPS's global footprint—including formulation sites in the US, UK, and India—is a core differentiator. What are the complexities and advantages of coordinating formulation development and manufacturing across these geographies, and how does that influence your ability to shorten client time-to-market while maintaining quality, regulatory compliance, and cost efficiency?*

Brad: All sites use the same Stage Gate approach in product development, and each project team uses that guidance to ensure compliance and consistency across sites. It is especially important where there's an integrated project that spans across two, perhaps even three sites. Where one site may have a piece of equipment that differs from another site, we use SUPAC guidance and appropriate material characterization to demonstrate equivalence. Lastly, the development scientist(s) or MSAT team at the developing/transferring site will literally travel to the scale up/commercial manufacturing site to ensure proper translation of manufacturing technology.

CP: *Formulation challenges are expanding beyond traditional small molecules into areas like peptides, oligonucleotides, and other complex modalities. How is PPS positioning its formulation R&D capabilities to support these newer classes of therapies, and what unique hurdles do you see in bringing them from lab to clinic?*

Sunny: Each modality is unique and does not pose the same challenge. The challenge varies based on the nature of the formulation and intended target for delivery. At Piramal, we work towards enhancing the stability of these sensitive biomolecules by developing a robust lyophilization compatible formulation incorporating appropriate cryo-protectants and stabilizers/bulking agents early in the formulation development stage. Having these sensitive products in a lyophilized form enhances the stability / shelf life and eliminates the complex logistics associated with a frozen drug product.

The challenges one faces formulating complex modalities are i) complex multi-step compounding process; ii) tight in-process controls; iii) requirement of sophisticated equipment; iv) advanced analytical techniques to characterize; v) transfer from lab to larger scale GMP manufacturing and vi) Limited stability/ shelf life.

CP: *Sterile drug product manufacturing is a high-growth area for CDMOs, with unique formulation and scale-up challenges. From your perspectives, what are the biggest formulation and development considerations for sterile injectables today, and how is PPS building out capabilities to support sponsor companies in this space?*

Sunny: Delivering a safe and effective injectable drug product assuring sterility has always been a challenge for CDMOs involved in sterile injectable manufacturing. With the advent of complex modalities such as oligonucleotides and biologics (mAbs, ADCs), developing a robust formulation that can be successfully scaled up with suitable stability is the need of the hour.

With most biologics moving toward a lyophilized presentation, Piramal recently invested approximately $90 million in a new sterile manufacturing expansion in Lexington KY, including two large commercial size lyophilizers and a third isolator-based high speed filling line. Also, we lowered the barrier to developing/scaling up lipid-based complex modalities (lipid nanoparticle, nano-emulsions, liposomal) at our facility by investing in complex equipment such as high-pressure homogenizers (microfluidizers) and high-pressure extruders to achieve a desired particle size distribution (nm range). We continue to enhance our analytical capabilities to characterize and test complex matrices to better understand degradation pathways. Finally, by proper design of experiments (QbD/DOEs) in the R&D lab, our teams are able to successfully transfer the complex formulations to the manufacturing floor. **CP**

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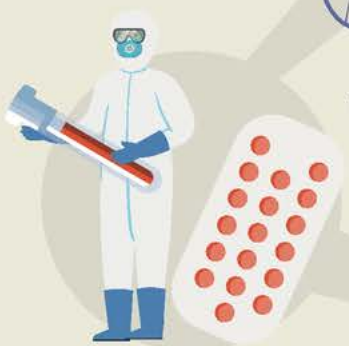

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