ROUTE SCOUTING, PROCESS OPTIMIZATION, AND SCALE-UP CONSIDERATIONS: DRUG DEVELOPMENT FIRMS AND CROs

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The current landscape for drug development has changed from decades ago when in-house "big pharma" candidates dominated clinical trial pipelines. While the largest pharmaceutical firms in the world still possess the rights to most investigational new drugs (INDs) undergoing clinical trials, many candidates have been plucked from either the development groups of aggressive, private-equity backed start-ups or spin-offs from IP-laden universities. And, these candidates- as well as those driven through clinical trials by independent start-up outfits themselves- typically still require extensive efforts regarding route scouting and final synthetic route selection, final process optimization, and successful scale-up of the selected route of the promising drug substance molecule. The right CRO partner proves invaluable for all three of these objectives.

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ROUTE SCOUTING AND SELECTION

While initial drug development efforts focus solely on synthesizing and isolating the molecule of interest, the focus shifts very quickly to identifying a feasible synthetic scheme for efficiently preparing material. Route scouting initiatives address this, as experienced CROs will concurrently and efficiently evaluate various methodologies for achieving the same end molecule. For instances where a synthetic coupling step dominates the preparation, a *convergent synthesis* approach leveraging fragment coupling and independent but concurrent synthesis efforts could prove vital for success. However, determining the best route takes into account many other factors including: effective and regulatory-friendly solvent selection, hazardous waste minimization, high-yielding reaction steps, reduction of the number of synthetic steps required, IP considerations, and ultimately cost controls. In a holistic sense, sustainability of the process for preparing the drug candidates remains paramount, and a well-organized and highly skilled approach to route scouting accomplishes this!

PROCESS OPTIMIZATION & SCALE-UP CONSIDERATIONS

An optimal CRO partner realizes and understands that process optimization and successful scale-up are *not* mutually exclusive. Rather, integration of the two occurs in lockstep as the selected drug candidates transitions toward process validation status. First, the best CRO partners properly advise drug development companies on important optimization and scale-up considerations, including (but not limited to): raw material availability, commercial equipment compatibility and capacity, safety and regulatory compliance requirements specific to the process, and key analytical chemistry/ impurity profile considerations for the anticipated commercial product. Reviewing and addressing all such factors allows the manufacturing process to be optimized at a representative scale in the pilot plant. Ultimately, this leads to a consistent, validation-ready process as the candidate progresses toward commercialization. Further, depending on the strategy of the drug development firm, it may be crucial that the partner CRO providing both route scouting and scale-up services ALSO possesses the capability to produce commercial quantities of material. The ability of a CRO pilot facility to mirror its own full-scale production capabilities may offer the advantage of minimizing future technology transfer risk.