

Perspectives on Accelerated Early Drug Development Using Precision Neat Drug Substance Filling Equipment

Twenty years ago, the formulator on a drug development project team might be asked “when clinical supplies would be available for clinical studies?”. Over the years, this has evolved to the statement that “clinical supplies WILL be available by a given date because of pressing business demands and clinical studies are scheduled”. These conversations are reflective of pressures that shape contemporary drug product development practices. It is not a phenomenon that is isolated to cash flow challenged virtual companies that must satisfy anxious investors. Big Pharma is not isolated from this pressure and has aggressively reduced the lead time and cost of early clinical studies.

Not wanting to be the dreaded “critical path activity”, product development teams have instituted new approaches for supplying drug product to meet aggressive Phase I clinical study start dates. Precision equipment that can accurately fill hard gelatin capsules or vials with neat drug substance, have become an often utilized approach to meet aggressive timelines and cost reduction pressures.

The old adage that there is “no free lunch” applies well in utilizing such manufacturing approaches. The use of automated filling equipment for early studies defers, but does not eliminate the need to conduct formulation development. It is critical to weigh carefully the impact on the overall development plan of using neat drug substance filled capsules/vials vs. a formulated product in early studies.

Dosing neat drug substance brings some compelling advantages to a development effort.

- **It may be possible to file an IND sooner.** For dosing neat drug substance, only a limited feasibility study is typically necessary prior to manufacture of clinical supplies. In contrast, the development of a formulated hard gelatin capsule requires a number of studies that add time and costs to the program (e.g., excipient compatibility, formulation selection, process development). Dosing with neat drug substance can often reduce the lead time to initiate clinical dosing to 3 months from initiation of the project.
- **Development costs can be lower due to the need for fewer formulation development studies.** In addition, the analytical chemistry method development and validation costs are typically much less than that required for a formulated product. The lack of excipients removes the need for excipient compatibility testing blend homogeneity, and reduces the scope of prototype stability studies. Analytical methods development become simpler and less expensive. Dosing drug substance can be accomplished using dedicated change parts which removes the need to develop, validate, and perform equipment cleaning verification studies. In addition, there are no excipient acquisition and release testing costs.
- **There is a lower risk of technical problems that may delay availability of clinical supplies.** The lack of added excipients and simplified manufacturing process significantly reduces the potential issues of blend homogeneity, excipient interactions, analytical difficulties, manufacturing process problems, and product instability.
- **A drug compound with significant development issues can be terminated sooner and at lower cost.** This is primarily due to the reduction in capital outlay for the executed work. The ability to lower the cost of a failed program also lowers the opportunity cost of foregone development opportunities.
- **The development of dosage forms for use in downstream (Phase II/III) studies may be accelerated.** Dosing with neat drug substance in Phase I does not eliminate the need to develop a formula and manufacturing process for later phase development and commercial requirements. Given the availability of adequate drug substance quantities, it is possible for the more aggressive organization to initiate development of commercial-potential dosage forms at an earlier time.

- **Clinical supplies for toxic and highly potent compounds can be more safely handled.** Preparation of clinical supplies for a formulated product typically requires significant processing steps such as milling, blending, screening, granulation, and filling. Each of these steps presents a risk for raising drug-laden dust. The dust becomes an exposure danger to workers, an extensive equipment train, and the manufacturing facility. The manufacture of neat drug containing products reduces the exposure to a dedicated filling head within the apparatus. In addition, the entire apparatus is typically contained within an isolator to reduce exposure to workers and the manufacturing facility. Since full toxicology information is not typically available in early development, a simplified and better contained formulation and manufacturing process are important considerations to assure worker safety.

Along with the benefits of neat drug substance dosing, one must consider the disadvantages that accompany the approach. Some of these downside issues are actually corollaries to the above stated benefits.

- **Neat dosing of drug substance may have difficulty meeting the product quantity requirements beyond Phase I/IIA studies.** As studies enter Phase II and beyond, the issues of manufacturability for larger studies make neat drug substance dosing inadequate to the task. The equipment requirements for high speed encapsulation or dosage form change (e.g., hard gelatin capsule to tablet) necessitate that deferred formulation and process development studies be performed.
- **Neat dosing of drug substance can result in greater total development costs.** Since this approach defers rather than replaces the pharmaceutical development work needed to supply later phase clinical and commercial product, it is additive to the total development costs. The added costs are typically minor when taken in context of a typical development program, but should be recognized as not providing a formulation “free ride” through development.
- **Not all drugs are suitable candidates for neat dosing of drug substance.** It is essential that basic biopharmaceutic and physicochemical properties of the drug substance be evaluated for suitability to the approach. Drugs with inadequate bioavailability may require formulation and manufacturing process intervention to achieve adequate absorption. In addition, an increase in drug bioavailability due to formulation can significantly decrease the quantity of drug substance required to supply clinical studies. Since the supply of drug substance can be rate limiting in the initiation of early clinical studies, removing this drug substance bottleneck can actually decrease the time requirement to enter larger studies and significantly reduce program costs for drugs with complex and expensive manufacturing processes.

In final analysis, the strategic and tactical decisions for conducting a pharmaceutical development program become ever more complex as the business, regulatory, and scientific demands escalate. The manufacturing of early clinical supplies by automated dispensing of neat drug substance into capsules or vials provides an attractive approach to shorten the lead time for acquiring essential clinical data. However, the downstream implications for later stage development must be carefully weighted in light of the total picture of corporate needs.

AAIPharma Services has participated in the development of drug products for the pharmaceutical industry for over 25 years and brings a deep understanding of differing perspectives and needs of its customers. AAIPharma Services has the Xcelodose 600S automated powder dispensing equipment available to clients for whom this approach is an attractive business and scientific approach. We invite you to discuss your particular needs with us. Together, we will determine the most advantageous route to achieve your scientific and business needs.