Automating the Preparation of Test Articles and Clinical Trial Supplies

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The pharmaceutical development director of today is under enormous pressure to progress new molecules through early phase development as rapidly as possible and at reasonable cost. In research, great progress has been made to reap the benefits of combinatorial chemistry and to provide potential new chemical entities (NCEs) for the company pipeline. For all leading pharmaceutical companies investment in research is high, but costs escalate further when the molecule enters the full development phase. Recent estimates indicate that a delay of just a single day can cost a pharmaceutical company between US$1 million and US$13 million in lost sales, and that the development process itself costs US$30,000 per day and is rising by 10 to 12 per cent per annum (1).

It is crucial that strong NCE contenders for commercialisation are identified early on and receive full development support. Conversely, it is important that molecules with less promising or even no therapeutic potential at all are removed from the pipeline early to free up development resources for better drug candidates. For these reasons the decision taken by a company to move an NCE from the research phase to the development phase is vital for managing the success of the company. Preclinical and early clinical trials provide pivotal data for this decision process. The sooner these trials can be completed, and the higher the integrity of the trial results, the sooner the company can make this decision with conviction. One method of facilitating this process that is generating much interest in the pharmaceutical industry, is the automation of the preparation of test articles and early clinical trial supplies, and the focus on preclinical studies on the drug substance alone. Newly available automation technology can achieve these aims and bring significant benefits.

PREPARATION OF TEST ARTICLES FOR PRECLINICAL SUPPLIES

Preparation of test articles for preclinical supplies is typically labour-intensive, tedious and often inaccurate. Often, qualified scientists spend many hours hand-filling test substances into individually weighed capsules or other containers. Typically, the weight of each dose is pre-calculated and the technician must prepare these on a regular basis, perhaps weekly, throughout the trial. If the trial is a dose ranging study, then this will add further complications.

The scheduling of the trial is influenced by the availability of skilled staff and laboratory equipment to prepare the test article. Although this is certainly true of the smaller preclinical units, even the largest contract houses report that only a limited number of such trials can be scheduled at any one time due to the lack of availability of skilled staff. The time required to complete such trials can be lengthy and staff costs are high.

Additionally, in early stages of the development process, the amount of drug material available may be a limiting factor, particularly in the case of biologically active materials or high cost compounds. Quantities as low as a few hundred milligrams may be all that the research technician has available for the required studies and therefore minimum wastage is paramount.

PREPARATION OF EARLY STAGE CLINICAL TRIALS MATERIALS

There are additional problems for early stage clinical trial supplies. The task of filling hundreds (or even thousands) of capsules by hand with minute quantities of drug within defined levels of precision has rightly been described as ‘the job from hell’ as it is highly monotonous. The task is also something of a double-edged sword; because of the need for accuracy and reliability, it is a job that requires the skilled input of a trained technician but one which offers little in the way of job satisfaction.

Furthermore, there are important quality issues that need to be addressed. When trials require many thousands of these individually weighed supplies, the human error rate may become significant as even the best-trained staff struggle to remain attentive to detail for such prolonged periods of repetitive work.

BLENDING WITH EXCIPIENTS

When preclinical and clinical trial supplies are filled manually, large dose weights of drug substance are usually weighed directly into the containment system, but smaller dose weights (below about 20mg) of drug substance are often blended with a bulking agent. This, however, adds a time and risk factor to the studies, because drug compatibility with the excipient must be predicted and then verified through stability studies. The blending of the drug substance with an excipient may more than double the overall time to complete the trial. The formulation and stability-indicating analytical methods must be developed, and the blend must be manufactured and tested for homogeneity. Furthermore, the stability study must be completed to ensure the test article is representative of the original drug substance. Homogeneity testing may need to be repeated on several occasions to ensure that the blend consistency remains constant.

Blending adds complexity to the clinical trial process. The blending process itself may be difficult to achieve with the degree of reproducibility required. Other typical problems might include analytical errors leading to results that are not representative of the sample collected for analysis due to poor sample splitting, dilution errors, improperly prepared standards, weighing errors, and container tare or vial-cap errors (2).

Another disadvantage of blending is that the excipient may mask the effect of the drug substance in the trial, leading to erroneous or misleading results. Although rare, such instances can be very costly. Occasionally, the use of an excipient has caused a trial to fail because the test substrate has become unstable. Removing the need for bulking agent therefore has significant advantages when conducting preclinical and early clinical trials.

Preparation of preclinical and early stage clinical trials supplies should be automated. The automation of the filling process for these supplies has many advantages. For example:

- The study can be more easily scheduled in accordance with the study director or clinician's needs
- Resource requirements are reduced
- Risk is reduced by removing human error from the process
- Automation can also reduce the problems of material inconsistency and environmental impact on the filling process
- Automation can reduce the time for supply of clinical trial material and hence the critical data required for decision-making is available sooner

The advantages of automatic filling are even greater when pure drug substance rather than blended material is used. The problems outlined above regarding blending may be eliminated if a drug-only formulation is employed. In order to do this a technique must be adopted that will enable the technician or research scientist to handle small quantities of drug with confidence and precision. The advantages of eliminating the need to handle drug-excipient blends are potentially enormous, in that weeks or even months of stability and validation work can be avoided.

This will have a positive impact at all levels of the organisation:

- **Laboratory Staff** – The technicians' work is made easier by not only removing the monotony of manual filling, but also by considerably speeding up the process, which allows more value-adding work to be carried out. The reduction in technician time and resources in carrying out stability work and its subsequent validation is even more significant. The possibility of technician error may be greatly reduced, which in turn reduces the risk of trial failure.
- **Middle Managers** – A reduction in the time taken to produce clinical trial supplies enables greater throughput. Automation also offers the chance of improved resource management, with valuable technician time being freed up for other tasks.
- **Senior Management** – Better optimisation of assets and resources. Most importantly, for a pharmaceutical company, a reduction in preclinical and clinical trial timelines can mean increased speed to market, facilitating competitive advantage or increased sales. In the case of clinical research organisations, the ability to offer better service in terms of accuracy, reliability and greater throughput provides market advantages.

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REVIEW OF AUTOMATED SYSTEM METHODOLOGIES

The case for automation in the handling of clinical trial supply manufacture is a strong one, but begs the question, what is currently available on the market? The answer is surprisingly little, for two main reasons.

Firstly, most equipment suppliers that cater for this market sector have not been able to combine the fill speeds offered with the precision required. The precluding factor has been the

ability to handle very small quantities (for example, sub-milligram quantities) of drug powder required, accurately and consistently enough to offer any real advantage to the pharmaceutical development process.

Secondly, most manufacturing equipment suppliers have tended to cater for the high volume sector of the market for production purposes post-launch. The clinical trial supplies market is small and therefore unattractive to the larger manufacturers of equipment.

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TECHNOLOGIES FOR FILLING SMALL DOSE WEIGHTS

To date, all methods for the metering of drug and drug formulations for filling capsules, for tableting, or for dispensing into other containment systems, have used a 'volumetric' approach using dosator, auger and other feeding systems. Other technologies with the potential for dispensing small dose weights of drug have been investigated. Some of these include the use of ultrasonic and electrostatic methods (such as Delsys and Phoqus) for dose dispensing. Although the latter technologies have the potential for very accurate dispensing, they only perform satisfactorily with well-conditioned powders of known and well-controlled physical properties; they are quite unsuitable for the range of NCEs that are routinely evaluated in preclinical and clinical trials. Where particle size distributions of the material are known with reasonable accuracy, particle-counting techniques could theoretically be used, although to date it is not believed that this approach has been developed.

Gravimetric dispensing has been used, but in the past this has been a very slow process. It does, however, have the advantage of providing a very simple validation route for dose uniformity, since each dose is individually weighed.

Gravimetric filling may be the only satisfactory solution that will give drug development and formulation scientists the control and precision required to meet their needs with accuracy and reliability. The number of such systems on the market is limited. The systems available vary considerably in their features and benefits. The main factors are:

- Type of receiving dosage container (capsule, vial, tube and so on)
- Dose container throughput; the filling rate, usually expressed as units/hour
- Automated or manual dose container handling
- Ability to handle different container sizes
- Weight range bandwidth
- Precision and accuracy
- Ability to deal with a range of powder characteristics
- Control systems; the recording of dose weights
- Level of validation for regulatory needs (CFR 11)

The main differences between the systems available are the form of the dosage container offered (capsules, vials, tubes and microtitre plates) and the range of weights that the systems are capable of handling, but usually with a trade-off between precision and speed of fill.

One new system also allows a programmable level of precision whereby greater precision can be achieved with slightly slower fill speeds, even at fill weights as low as 100 micrograms. A predictive control algorithm is used that reduces fill cycle times. The system stores all relevant information on batch characteristics and sample/product identity, and individual fill weights are recorded with GMP-compliant software.

The continuing development of such systems falls in line with software-controlled laboratory equipment, and the prospective buyer can expect to see further automation and sophistication in the control systems, which should offer increasing precision and fill speeds. This may develop to the point where such technologies may begin to have applications in manufacturing as well as laboratory use.

The pharmaceutical development director of today has a major opportunity. Automated dosing systems can offer the pharmaceutical company or CRO real advantages both in terms of resource savings (time, money and human) and reduction of risk – resulting in faster time-to-market. In the eyes of the pharmaceutical technician, eliminating the 'job from hell' allows for greater job satisfaction and the opportunity to carry out more value-adding work.

From the perspective of the pharmaceutical company, automation of preclinical and clinical trial supplies can provide one step towards increasing speed to market. ◆

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