Shortening Timelines to Phase I Formulation

With micro-dosing technology, the number of process steps involved in taking a new drug into clinical trials can be reduced, enabling new drugs to enter the clinic more quickly and failed compounds to be weeded out earlier – resulting in valuable savings in clinical expenditure.

DRIVERS IN THE CRITICAL PATH

With the introduction of the US FDA’s Critical Path Initiative in 2004 (1), any areas in which timelines can be reduced in the drug discovery and development process are now in favour. One strand of the Critical Path Initiative is to reduce the time and resources expended on candidate products that are unlikely to succeed. For drug candidates to essentially ‘fail faster’, new tools are needed to distinguish those candidates that hold promise (the prize dogs) from the runts of the litter that do not earlier on in the process. Thus far, the FDA has identified and published a list of six topics and 76 opportunities in the drug discovery and development cycle, including in vitro tests, computer models, qualified biomarkers and innovative study designs, that could be used to reduce timelines to evaluate and predict the safety and effectiveness of drug candidates, as well as determine how easily they can be manufactured (2).

One area that so far has not been investigated extensively is how to shorten the timelines for progressing compounds from the preclinical stage to Phase I. Currently, it takes an average of 12 to 18 months to get a new chemical entity (NCE) into Phase I clinical studies, due largely to a number of process and manufacturing issues such as formulation and stability studies of how the raw active pharmaceutical ingredient (API) reacts when it is mixed with solid or liquid excipients. However, if an API could be tested directly in Phase I studies to find out how effective and safe it was, and it failed the trial at this point, out-of-pocket clinical costs would be substantially reduced compared with if the drug failed in Phase III trials.

Testing an API directly can be problematic, as it often requires so small an amount of material in each dosage of the formulation to be tested that it is difficult to dispense. To overcome this problem, pharma companies can weigh the API into bottles by hand and re-suspend the compound in water or methylcellulose so that enough of
the drug can be dosed. This approach has drawbacks, however. First, it means giving a skilled technician a time-consuming, error-prone task that has limited traceable documentation as it is difficult to determine how much API dose is in each bottle and how much of the dosage was left in the bottle after the patient received it. This lack of an audit trail can sometimes be viewed unfavourably by regulators. Additionally, patients often dislike the taste of the API in water or methylcellulose, and this can lead to compliance issues with the trial.

Another different challenge is that nearly two-thirds of newly synthesised APIs have poor solubility (<0.1mg/mL) (3), making it hard to produce suitable liquid formulations. One solution to all of these issues is to use automated micro-dosing techniques to fill capsules directly with the API in powder form (4). This approach is increasingly being cited by pharma companies and CROs as the quickest and best option for getting APIs into Phase I trials. Water-soluble APIs are well suited to direct filling into capsules, and fewer soluble compounds often also work effectively when in capsule form. With pharma companies under increasing time pressures to reduce pre-commercialisation research and development timelines, they would rather fill a capsule with pure API powder than spend time making a specific formulation.

**AUTOMATED MICRO-DOSING**

Directly filling a capsule with an API offers the benefit of not needing to spend time carrying out excipient selection studies; this can potentially take three to six months off the time taken for formulation and stability testing requirements (4). In the drug development department of a major US pharma company, one type of micro-dosing system (the Xcelodose® 600 Precision Powder Micro-dosing System, see Figure 1) is being used to reduce the number of process steps involved in taking APIs into clinical trials. This system works on the ‘pepper shaker’ or ‘pepper pot’ principle, in that when you shake a pepper pot it will dispense a specific amount of powder according to how many times it is tapped, as well as the size of the openings in the pot.

The micro-dosing system contains a dispensing head with a mesh containing holes of specific diameter through which the powder passes. After one dispense cycle, the powder forms micro-bridges and will not be released from the head unless the head is tapped. The head is attached to a tapper arm and solenoid integrated to a computer. The solenoid sends signals to the tapper arm, which taps the head, and this then dispenses the powder into the capsule; the amount of powder dispensed is a function of the number of taps that the dispensing head receives. The capsule is placed on a seven-figure microbalance, tared to zero and dispensing commences; when it has reached its target weight, the tapping ceases. This simple process can fill around 600 capsules per hour with validated quantities as low as 100 micrograms with a two per cent relative standard deviation (RSD) weight range (5); additional reports indicate that studies using API amounts as low as 10 micrograms are under evaluation.

The micro-dosing system has two important features. First, it checks every capsule weight and allows for setting acceptance and rejection parameters, thus eliminating a weight-sorting step; the weight-checking traceability, which can be printed out, simplifies the capsule count required at the end of the batch for yield calculations. Second, the system will compensate for differences in powder behaviour by altering the number of taps, until the target weight is reached.

**PROCESS DEVELOPMENT**

Experience at a major pharma company has shown that micro-dosing API directly into a capsule eliminates many of the process and administration steps involved in getting some drugs into Phase I trials. Specifically, micro-dosing of API without any excipient reduces the need for developing dissolution methods or content-uniformity testing. An additional benefit is that the time required for analytical method development to test these parameters is also decreased. Another area where timelines are reduced is that of formulation development since there is no need to order, test, release and produce documentation on the excipients that would have been required to make a blended formulation.

A team at the pharma company was also successful in developing a method to produce capsules containing API powder only. Initially, the API is visually inspected for bulk density issues and agglomerates, which could clog the dispensing heads of the micro-dosing system. If these are detected, then one or more pre-processing steps are undertaken such as sieving, milling or roller compaction according to published methods (6).

The team used a test run of 30 capsules, estimating the size of capsule required for the amount of API. Generally, they filled 50 milligrams of API powder into a size three or four gelatine or hydroxylpropyl methylcellulose (HPMC) capsule, and then estimated the tap rate required to fill the capsules by using their database of APIs and excipients to predict how the new API powder
would flow. The database contains information on API powders with two to 50 microns bulk density, and on particles that are round, flakes or fibrous shapes.

The Xcelodose micro-dosing system has 31 different dispensing heads, and so the development team performed a limited run of 30 capsules and then evaluated the length of time required to fill each capsule, as well as the capsule rejection rate. If the run took longer than 30 seconds, then a dispense head with a mesh containing larger holes would be selected, or stainless steel dispense fingers (see Figure 2) would be added to the powder within the dispense head to allow the API powder to be broken down while filling took place. This method development is quick to complete and, according to the drug development team, micro-dosing capsules directly with API powder represents a viable way to reduce the number of personnel required for filling capsules; provides a better process understanding and – most importantly – offers a faster route to Phase I trials.

CONCLUSION

Automated micro-dosing of API powder in a capsule offers a good option for getting drug product into the clinic in a short period of time. The method is capable of supporting early clinical studies and may help to weed out those compounds that will not make it through trials sooner in the clinical phases of development. The whole process also falls in line with many pharma companies’ biotechnology investment strategies because use of a micro-dosing system facilitates minimal investment in a compound until it is known whether or not the drug has a good chance of making it to market. Ultimately, the increased efficiency achieved using an API directly in clinical trials could result in highly effective new therapies reaching patients more rapidly, thus fulfilling a key tenet of the FDA’s Critical Path Initiative.

References

2. FDA’s Critical Path Opportunities List www.fda.gov/oc/initiatives/criticalpath/reports/opp_list.pdf
3. Dubin CH, Drug Del Technol, 6 (6), pp34-38, 2006
5. Xcelodose® S Precision Powder Micro-dosing System www.xcelodose.com

Figure 2: Stainless steel dispense fingers for use with cohesive API powders

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