Accelerating Drug Development with Precision Dosing Techniques

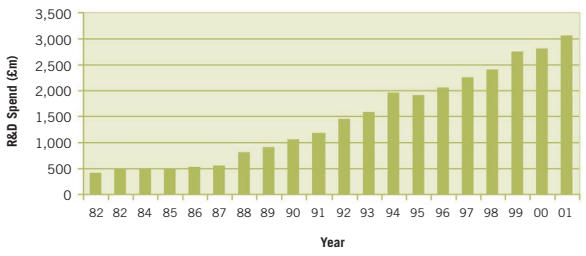
By David Edwards, Director of Xcelodose™ Business Unit at Meridica

David Edwards is a founder member of Meridica and is responsible for Meridica's position in the marketplace and its business development. He has over 20 years' sales, marketing and business management experience in the pharmaceutical and health care industry, in companies such as Hoffman LaRoche, Aspro-Nicholas Laboratories and Brooke Bond Oxo. He has worked extensively with the City, particularly in the biotechnology sector, where he has managed a number of due diligence programmes in support of IPOs and venture funding.

Pharmaceutical drug development takes too long and is too expensive. With a patent life of 20 years, and the gestation period for an NCE from research through to launch being of the order of 10-12 years (providing it survives the huge rate of attrition), the actual time to recoup the R&D investment is often only six to eight years. It is also well-recognised that each extra day that a product is on the market may well equate to $1million in additional revenues for a global product. Any reduction in the time taken to complete development will be beneficial, both in terms of additional revenue and also competitive position.

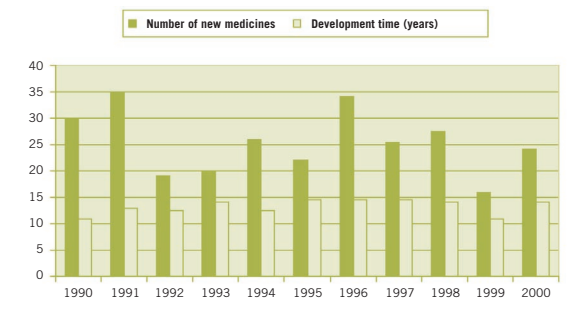
Speeding up the development process (and thereby reaping the rewards) is seen as the 'Holy Grail' within the industry. In the last 15 years, every company with an active R&D department has carried out numerous initiatives for speeding up its development process and whilst there have been some notable improvements as a result, the law of diminishing returns is beginning to apply.

Figure 1: R&D Investment in UK Pharmaceuticals



Source: Centre for Medicines Research International

Figure 2: Numbers of New Medicines Introduced and their Average Development Time



Source: Scrip

Is there anything left in terms of scope for improvement in development timelines? Pharmaceutical companies have tried throwing extra cash into R&D (see Figure 1), but this has not achieved the desired result (see Figure 2).

Jean Pierre Garnier, CEO at GlaxoSmithKline (GSK) recently suggested that the number of GSK projects entering the first phase of human clinical trials would be doubled during 2004 and those entering Phase II would be tripled. This, on the face of it, is an amazing statement. In terms of revenue, GSK is the second largest pharmaceutical company in the world and, as such, its pockets are much deeper, funding the resourcing of such a significant increase in development products coming through the pipeline. However, as can be seen from Figures 1 and 2, this does not necessarily confer an advantage.

If the increase in throughput is due neither to a higher level of funding alone nor to a slicker process, how would this quantum leap in throughput be achieved? The answer is the use of breakthrough technologies; as Garnier points out, "the use of new technologies had in some cases taken two years off the time needed to get a molecule into clinical trials". This latter point is well-recognised; his stated intention of removing two years from the development process is of major importance to GSK and would provide a real competitive edge.

One such area where breakthrough technologies have recently been applied to give faster development times is via high-precision dosing for formulation and the manufacture of early-stage clinical trial supplies. This includes the dosing of drug into capsules for Phase I and IIa clinical studies, formulated product for oral delivery and capsules for inhaled delivery. High-precision, accurate dosing uses less pharmaceutical ingredient and is faster than traditional approaches.

PRIMARY OBJECTIVES IN DEVELOPMENT AND SUPPLY OF PHASE I CLINICAL TRIAL MATERIALS

The overriding objective for quality is not a subject for debate. However, other objectives, such as speed of delivery, dose flexibility, stability and drug consumption (that is, the amount of drug used) are all variable. Getting the drug candidate into Phase I as quickly as possible enables the development team to assess the candidate compound and compare its potential for success with other candidates in the class. Those that are deemed to have less chance of succeeding can be more rapidly eliminated from the company's development portfolio, enabling R&D funding to be focused more effectively.

As if the challenges described were not enough, the drug dose will remain uncertain right up to the start of Phase I. Because of this, companies often need to formulate a range of doses that may present formulation or processing problems. For example, where the anticipated dose range is narrow, it may be possible to support clinical dosing using a common blend approach. However, where there is scope for a wide range of dose levels, it may be necessary to support the development of two unique dosage forms.

In all of this, drug consumption is important. In Phase I, more so than at any other point in the process, the amount of drug available may be extremely limited. Any technology that can minimise wastage in development, or utilise very small amounts of drug substance in manufacture, will be advantageous.

ROUTES TO REDUCING ACTIVE PHARMACEUTICAL INGREDIENT (API) DEMANDS IN DEVELOPMENT

There are several other ways to increase speed and flexibility of drug development. These include miniaturisation – scaling down all aspects of the formulation and process development by using techniques such as granulation (for example, small-scale high-shear equipment); compaction simulation or flow assessment by a combination of small-scale equipment and experimental design. One such example is use of the Bench Top FT4™ Powder Rheometer to assess flow performance of powder blends. This non-destructive test uses 10-20g of blend to determine likely flow behaviour. The material studied can subsequently be evaluated for compression and post compression behaviour.

Figure 3: Xcelodose™ 600 System

More fundamentally, some pharmaceutical companies will carry out a rigorous evaluation of the physical and mechanical properties of the powder, such as hardness, elasticity and fracture behaviour to give much 'smarter' formulations of solid dose forms, which are easier and quicker to produce. The objective in every case is to derive maximum data from each experiment, which will give confidence that the product will be manufactured successfully for the clinic whilst reducing drug demands compared with more conventional approaches.

ROUTES TO REDUCING ACTIVE PHARMACEUTICAL INGREDIENT (API) DEMANDS IN PHASE I MANUFACTURE

Conventionally, two approaches can be used to minimise the amount of API used in Phase I studies; both approaches rely on filling of drug substance alone into either a bottle (for reconstitution) or a capsule.

Dispensing 'drug in a bottle' is sometimes used – that is, drug with no added excipients, dispensed into a container, in this case a bottle. This allows dose selection at the point of manufacture. The drug is usually stable in a bottle where there is no glass/drug interaction and this in turn reduces the amount of stability testing work required. However, use of this rather labour intensive method may be limited as re-constitution is necessary. This may involve the addition of water to the drug, which can result in product degradation, or the use of cellulose-based suspending agent, which can be unpleasant to swallow. Furthermore, homogeneity may be an issue if the entire dose is not administered: the weight of the empty bottle may cause problems in balance selection, particularly if the drug weight is low. The use of dosator systems that dispense drug to bottles may be more suitable.

For these reasons, the alternative of filling API directly into capsules may be preferred, a process whereby the pharmacokinetics of the compound allow dosing in this way.

POWDER PRECISION DOSING – EQUIPMENT AVAILABLE

Automated powder precision dosing at very low weights was, until recently, not possible. Most pharmaceutical development departments filled capsules by hand – a time-consuming task that requires the steady hand of a skilled operator and enormous levels of concentration. The attrition rate of capsules outside the required accept/reject limits may be high and the attention span of the technician is limited. Most companies will not fill API at levels below 20mg by hand, opting to blend with excipients such as lactose, and then carrying out analytical tests on the blend. This will, of course, include stability testing over a period of time (three to six months) to ensure that the blend is homogenous, and that drug/excipient interactions have not occurred.

Automated capsule filling technologies are well-established today for manufacturing purposes and can fill at rates of 100s of 1000s of capsules per hour. However, the ranges of weight for

these systems are limited to approximately 20mg and above of formulated blend, and are, therefore, not suitable for the smaller runs and higher precision dosing used in the manufacture of early stage clinical trial materials.

BREAKTHROUGH TECHNOLOGY?

The need for a fast, accurate machine capable of filling very low weights for production of Phase I/IIa clinical trial materials represent an important angle in the market. For example, Xcelodose™, a new micro-dosing system, is remarkably straightforward. It employs the principle exemplified by the simple pepper pot. When a pepper pot is inverted, a small amount of powder is released and then the flow ceases. If the pepper pot is tapped, another aliquot is released. The powder flow ceases due to the formation of micro-bridges over the holes. These micro-bridges are broken or disrupted when the shock or 'tap' is applied to the side of the pot, thereby releasing more powder, the process can then be repeated. The amount of powder released per tap is extremely consistent and is largely a function of the characteristics of the powder and the size and number of the apertures through which it flows.

Within this system, the pepper pot principle is utilised via a dispensing head comprised of a small stainless steel hopper with a mesh plate at its base. The mesh plate contains a specific number of holes having a diameter dictated by the characteristics of the powder to be dispensed. The dispensing head is filled with (drug) powder and is situated at the end of a tapper arm and is connected to a seven-place microbalance, which is used to apply a tap to the head aligned over an empty container (usually a capsule). A computer controls the tapper arm a seven-place microbalance, which is used to monitor the weight of the capsule in real time. Having set a target weight, the software-controlled system taps powder from the dispensing head into the empty capsule, and then predicts how many taps are required to reach the desired weight. This is achieved with maximum accuracy using a number of rapid taps and then as the target weight is approached, the rate of tapping slows until the desired weight is achieved. The weight of the capsule (plus drug powder) is weighed constantly throughout the filling process, and then, finally, when the dispensing process is complete. The system can be used to fill drug powders in the weight range of 100 micrograms to in excess of 100 milligrams with RSDs of less than two per cent.

Both the pharmaceutical companies and the regulatory bodies are keen to see improvements in the quality of pharmaceutical development. Such micro-dosing systems facilitate this by ensuring that the weight and a complete log of all data for each capsule are recorded in a 21 CFR Part 11 compliant manner, enabling traceability and full audit trails for any filling programme. This, when combined with the speed of fill, and the ability to fill such low weights very precisely with minimal wastage, eliminates the need for blending and offers higher pharmaceutical standards. It reflects a technological step forward, which in turn can result in considerable savings in development time and costs.

WHERE FORMULATION IS REQUIRED

Developing products with drug-only formulations offers advantages in terms of time and speed of development. However, in some instances, formulating the drug may be necessary in order for the body to be able to absorb it, particularly if the API is poorly soluble. This may involve granulation with wetting agents, changing particle size parameters, or use of acidifiers. Inhaled products represent an example of the need for formulation in order to maximise the respirable dose.

Techniques used include the development of a base blend or granules with known stability to make one large batch, and then to fill according to dose requirements. This offers high yields, little wastage and good stability when used in conjunction with automated high-precision capsule-filling systems. If single stage capsule fillers are used, the yields may be much lower and segregation is more likely. The advantages over traditional common blend approaches are higher manufacturing yields due to precise dosing and the filling technology is more forgiving over automated encapsulation equipment. Most blends will fill using a micro-dosing system, even when the flow properties are poor.

CONCLUSION

The arguments for the use of automated, high-precision micro-dosing technology over traditional methods such as filling by hand or blending with excipients are powerful. The technique has been adopted by many of the leading global pharmaceutical companies to improve development timelines and speed up the go/no go decision-making process for drug development.

The key features are:

- Flexible through the ability to dispense drug substance directly into capsules, bottles, blisters or vials
- Minimisation or elimination of the need for early formulation development and an associated reduction of stability testing
- Reduction in the amount of drug substance needed to get to 'first in man'
- Reduction in analytical development costs during the early part of the programme
- Adaptable and flexible equipment, suitable for GMP manufacture of oral and inhaled clinical trial dosage forms

Combining these features with increased speed of production over manual methods and greatly improved quality of data to meet the needs of the regulatory authorities, makes the argument for use of such breakthrough technologies in pharmaceutical drug development hard to contest. ◆

The author can be contacted at david.edwards@meridica.com.