

Capsule filling challenges

Safe and cost-effective workflow solutions for clinical first-in-man studies

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Filling capsules is a very common activity in clinical first-in-man studies, but exactly how this is carried out typically depends on the throughput required and the resources available.

For early clinical trials (phase 0 and 1) the objective is to evaluate a drug’s delivery method and dosage regimen, and studies typically last up to one year. Trials are usually managed internally by the pharmaceutical company’s toxicology department or outsourced to specialist contract research organizations (CRO’s), such as CoreRx, Inc.

Depending on the nature of the drug and test subject, new pharmaceuticals are often administered via gelatine capsules. Filling capsules is often carried out manually, either because sample series are too small for filling machines or because different amounts are required per capsule, which is not easy to automate. This necessitates manually weighing highly potent, hazardous substances precisely with a spatula, which is tricky and challenging. As the materials used in clinical studies are usually of unknown potency, any spillage or exposure presents a safety risk to the scientist.

First-in-man trials are strictly regulated by the United States Food and Drug Administration (FDA) and require capsules for phase 0 and 1 trials to be filled under sterile conditions. Therefore, any substances that come into contact with the drug must be sterile and made of an FDA-compliant material. Good Laboratory Practice (GLP) must also be applied which demands reproducibility, traceability, and full documentation.

Common challenges in development programs – a CRO perspective

CoreRx, Inc., a contract research organization (CRO) based in Florida, work predominantly on formulation development and analytical development projects for clients in the pharmaceutical industry. They frequently encounter similar challenges in the various development programs they undertake:

- Aggressive timelines. Often, urgent information is required up front on the feasibility of a new chemical entity as a drug, without having a fully stable formulation. Clients are keen to get a clinical result (early phase toxicology and animal studies, pKa studies, or tolerability in phase I human clinical studies), in spite of insufficient time to develop a fully-formulated manufacturable dosage form.
- Program has already begun. In these cases, original timelines are set, clinical dates are already known and scheduled, and the client is under pressure to get materials to put into the clinic with just a few months before their clinical time is scheduled.
- Limited quantities of drug substance available. Clients are often working with a new chemical entity, where the synthesis program runs concurrently with the early dosing studies. Early synthesis batches may be of the order of several grams, of which CoreRx may receive

Tab. 1 Filling specifications and results for range of capsule strengths

	1 mg Strength	3 mg Strength	9 mg Strength	0.3 mg (Blend)
Target yield	1,370 capsules	1,060 capsules	990 capsules	1,250 capsules
Target fill weight (mg)	1.14 mg ± 15%	3.42 mg ± 10%	10.25 mg ± 10%	20 mg + 7%
Acceptable Fill range	0.97 – 1.31 mg	3.08 – 3.76 mg	9.23 – 11.27 mg	20.0 – 21.4 mg
Reject rate	1.6%	1.1%	1.4%	0.5%
Manufacturing time	3 days	2 days	2 days	2 days
Encapsulation rate	58 capsules / hour	62 capsules / hour	62 capsules / hour	62 capsules / hour
Average fill (mg)	1.137 mg	3.372 mg	10.202 mg	20.215 mg
% RSD	6.68% (5.7%*)	3.78%	3.32%	2.26%

* RSD with rejects removed

a gram or less to work with. At this phase, the drug is expensive and precious, so it is important to avoid wasting any of it.

- Handling potent compounds. Companies are increasingly developing cytotoxic and potent compounds, and containment of these substances is a primary safety concern for lab managers and personnel.

Phase I clinical trial – dose range finding study

Here is an example of a dose range finding study, undertaken for a client manufacturing Phase I clinical trial material. The study required the manufacture of four batches of different dosage strengths – 0.3, 1, 3, and 9 mg – at approximately 1,000 capsules each. This project faced all the challenges described above: very tight timescales; clinical time already scheduled; synthesis issues at the manufacturer and therefore a limited amount of material available. In addition, containment was a major concern. The substance was not cytotoxic, but had a very severe physiological effect at very low doses. The compound was being developed for irritable bowel syndrome (IBS) with constipation and thus had a very strong laxative effect. The API itself had extremely undesirable physical characteristics for ease of dosing. It was an amorphous, filamentous material, which looked like cotton candy in a jar – very fibrous and with absolutely no flow. It had a bulk density of 0.04 gram per milliliter (g/mL). Using Quantos with a manual sample changer, size 0 HPMC capsules were prepared for the four fill strengths. The 1 mg, 3 mg and 9 mg strengths were weighed as neat API in capsule, but the 0.3 mg strength had to be achieved as a blend, because 0.3 mg was too low to accurately weigh on the Quantos balance. Several different diluents were evaluated before selecting mannitol, and the 0.3 mg strength was prepared as a blend of API in mannitol (1.71%).

Table 1 shows how precise and accurate the average fill rates were for these capsule batches prepared using the Quantos system. Reject rates were low – down to 0.5% and RSD's were good, particularly for the higher fill weights (10–20 mg targets). Note: The API strengths prepared include a correction factor which equates to 1.14 mg per milligram of active compound. Additional analysis of the 0.3 mg strength capsules containing the API / mannitol blend showed that the capsules were within specifications for content uniformity and no segregation was observed.

Cost benefits observed by implementing Quantos

Reduced labor time

Quantos, as a validated filling system, offered reduced labor time compared to manual filling in a Good Manufacturing Practice (GMP) regulated setting. A technician is capable of preparing 85–125 capsules per day manually in the lab filling 3 mg target weights (technician dependent). This compares to 60 capsules per hour using the system. The manual estimation is influenced by the specific standard operating procedure (SOP), but a manual fill in the GMP area requires the eyes of two technicians (second person verification). For this reason, it becomes very labor-intensive to put enough people into a room to fill capsules manually, whilst conforming to the SOP's, at a comparable rate to Quantos. The benefit of using a validated filling system is that only one operator is required to carry out the task.

Reduced development time

- Formulation development. Development time can be reduced by simply evaluating the compatibility between the capsule shell and the API, rather than focusing on excipient compatibility and fully formulating a dosage form.



Fig. 1 Quantos in 1:12 configuration with Ergodisc (semi-automated)

- Analytical method development. There is no need to qualify any specificity, as there are no interfering excipients. So, the analytical method for the drug substance can suffice for the drug product.
- Release testing. Typically, release testing would be performed on all incoming materials and all final dosage forms before release to the clinical side. Using neat API in capsule, the initial release determines the purity and potency of the API, which minimizes the back-end release testing and provides the opportunity to get the substances to the clinic faster.

Cleaning

Reduced cleaning requirements are another important benefit. In setting up a typical encapsulation machine, there are a number of product contact parts that have to be cleaned and verified, swabbed after dosing to show residual API left on the instrument. Quantos, with its self-contained dosing head, minimizes risk of spillage. The only potential product contact part is the sample changer. Even though all the material is dosed into the capsule shell and no spillage is observed on the carousel, the Ergodisc still must be washed and swabbed as it is in contact with the capsule shell. However, this is straightforward because it involves only one easily detachable piece requiring verification.

Safety – containment – material handling concerns

For projects involving cytotoxic or potent materials, Quantos offers a significant safety benefit. This system provides a good level of containment and reduces the potential exposure of the operators. This is due to the mode of operation of the dosing head, the precision with which it can dispense into capsules, and the fact that it is a self-contained unit. The drug substance can be stored in a standard jar or vial with the dosing head screwed on top. The whole vessel with dispensing head can be stored in the refrigerator if necessary. If the drug product is moisture-sensitive or oxygen-sensitive, this concept reduces the exposure of the substance to the ambient environment. It also minimizes any substance loss due to transfer from one storage or dispensing vessel to another. The design of the dosing head design offers flexibility for dispensing material with various characteristics.

Reduced waste or spillage is another benefit of using the Quantos system. If anyone has weighed manually with a spatula, especially very small quantities such as 1–5 mg, they will know that the amount lost or spilled can be significant. At this phase, when working with new chemical entities that can cost thousands of dollars per gram, it is important to avoid wasting any.

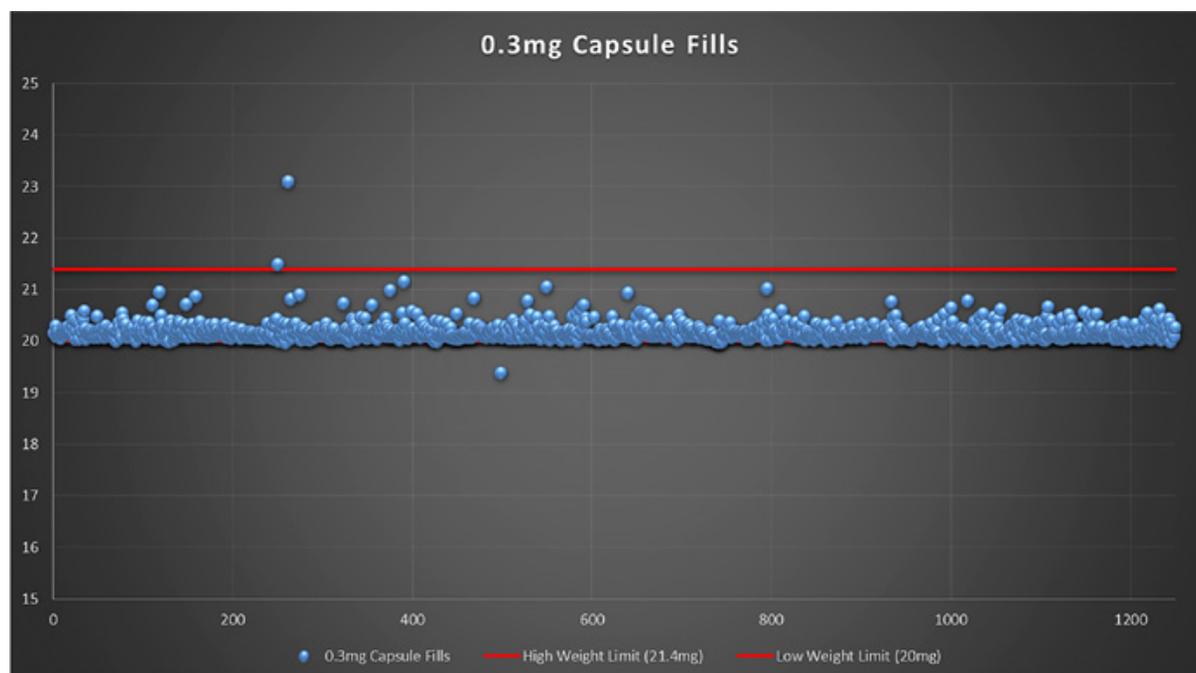


Fig. 2 Dosage weights of 0.3 mg strength capsules at target weight of 20 mg (1250 capsules).



Matthew Greene is a senior formulation scientist at CoreRx, Inc. in Tampa, Florida. He is also Assistant Professor of the College of Pharmacy at the University of South Florida. Matthew has 12 years' experience in pharmaceutical product development and has worked on the development of a wide range of pharmaceutical formulations and a diagnostic medical device. His current responsibilities include formulation and manufacturing process development, scale-up, and technology transfer of solid, liquid and semi-solid drug products. Matthew has considerable experience in solid-state characterization of small molecule drug compounds and their formulation into pre-clinical drug products for early toxicology and pharmacokinetic studies.



Joanne Ratcliff is communications manager for Laboratory Weighing at Mettler-Toledo. She specializes in automated powder dispensing and sample preparation applications. Joanne has 16 years' experience in automated weighing solutions for a range of laboratory applications in the pharmaceutical industry, including capsule filling and sample preparation for QA/QC. She holds a doctorate in physical organic chemistry from the University of Wales, Swansea.

Conclusion

CoreRx chose to implement the Quantos powder dosing system (from Mettler Toledo) to address their capsule filling challenges. Since 2009, they have been filling capsules (and vials) using a Quantos solution with a manual sample changer (Ergodisc). With its great flexibility, the system neatly bridges the gap between manual capsule filling and costly high-throughput filling machines and offers a significant and economical means of preparing early-phase clinical trial materials.

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An on-demand webinar is available on this topic at: www.mt.com/labtec-capsule

CoreRx, Inc. is a cGMP Compliant, FDA/FL DOH Registered, DEA Licensed (Schedule II – V) contract development and manufacturing organization based in Tampa, Florida. They specialize in formulation development, analytical development and clinical manufacturing of various dosage forms. The CoreRx ClinicFirst program is designed for clients requiring rapid supply of clinical trial materials for first-in-man (Phase I) clinical studies. The service offers API-in-capsule; blend-in-capsule; API-in-bottle; or blend-in-bottle, with an even faster to clinic option with ClinicFirstSM 60Day Guarantee.

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