

Paediatric drug product development through to commercialisation

How Almac developed a flexible paediatric dosage form using a robust manufacturing and filling process suitable for routine commercial manufacture.





Introduction

As a consequence of the EU Paediatric Regulation (EC1901/2006 and EC1902/2006) and the US requirement for inclusion of Paediatric Investigation Plans (PIP) in all new Marketing Authorisations, the demand for quality driven CDMOs with relevant knowledge and experience in the development and commercialisation of paediatric formulations is increasing. In recent years, there has been a notable shift away from the traditional route of administration for paediatric medicines, namely oral liquid formulations, to solid oral dose formulations such as granules and minitables. In fact, recent clinical studies have demonstrated that for children aged between six months and six years minitables provide equal, if not superior, acceptance rates when compared with sweet tasting syrup formulations, similar to those that have been historically used for paediatric patient populations.

Almac has been developing, manufacturing and packaging solid oral dose products for over fifty years and has previously commercialised several adult presentations for this market leading US headquartered client. Of particular importance to the client was Almac's experience with delivery of both clinical and commercial solutions from one integrated site at Craigavon (NI) combined with a track record in delivery of innovative packaging solutions tailored to our client's needs. Proven experience in the development of paediatric formulations was also a critical factor in placing the work with Almac.

Almac was tasked with developing an immediate release paediatric formulation to be packaged in a compliant, easy to use pack format. From the outset, the experienced client and Almac teams worked together to identify a target product profile and determine the best pack format for the product, one that would provide an economical commercial solution whilst also providing a high degree of fill accuracy in a consumer friendly package. The solution that best fitted the client's compliance and marketing needs was a "minitablet in stickpack" presentation.

The business challenge

From previous experience, Almac's formulators were aware of the challenges involved with the manufacture of minitables. The surface area/weight ratio of minitables is significantly higher than that of normal size tablets leading to higher ejection forces during compression, therefore, during development higher levels of lubricant were added to the compression blend formulation to offset any negative "sticking" issues that could potentially arise. The tablet design was also critical to the success of the project and was influenced by the proposed downstream activities i.e. filling into stickpacks.

Shallow convex minitables have better uniform density distribution throughout the core which can lead to a more robust compression process, however, the expert team also knew that deep convex minitables roll more effectively and therefore are more suitable for tablet counting technologies commonly used by sachet filling and encapsulation machine providers.



Utilisation of suitable compression equipment and tooling is also a key factor for successful delivery of minitabets. Multi-tip tooling is expensive so it is important that a reputable supplier with proven experience in multi-tip tooling design is chosen. Recessed dies are also advisable to protect punch tips. Effective control over the feedframe is critical as tablet ejection can be challenging. This requires an optimised set up, with precise adjustment of specially designed scraper blades being critical in limiting tablet jumping.

Similarly, the choice of sacheting machine is critical as ultimately this controls the unit dose being administered. With that in mind, Almac in partnership with our client, identified the Merz SBL50 as the stickpack machine most suitable for the project needs and for the future needs of Almac's client base. This machine is a single lane unit with a counting system that can operate at up to 80 cycles per minute.

The Almac solution

Through the Formulation and Process development stage, Almac was able to design a minitabset with characteristics built upon an acceptable trade-off between robust compressibility and effective processibility during the downstream sachet filling operation.

Utilising Almac's in-house Engineering team, Almac designed and fabricated a unique ejection blade with cover to overcome some specific issues which can occur with mini-tabs during the compression process. This, along with modification of ejection cams to optimise ejection height, resulted in a robust compression process suitable for commercial scale manufacture of the client's product. For this project, 37 tip multi-tip punches were fabricated allowing Almac to produce minitabets at rates up to 550,000 per hour.

As this project involved transitioning a development project through to commercial readiness, Almac assigned two dedicated, on-site Project Managers, one specialising in formulation and process development, the other with many years experience in Technology Transfer, commercialisation and ongoing management of commercial supplies.

Single site integration of Development and Commercial resources including Technical, Analytical, Quality and Project Management ensured scientific continuity and simplified effort, saving time and expense whilst reducing vendor management and mitigating risk to the overall project.

The Almac solution cont.

Key to project success was Almac's extensive experience with similar investment projects. Multiple visits to Merz facility, in conjunction with multiple visits by Merz engineers to Almac's site, ensured that all aspects of the equipment's installation, qualification and ongoing processing were discussed and addressed. Open three way communication between the Client, Almac and Merz allowed for seamless transfer of ideas and knowledge and ensured a stickpack solution suitable for the client's needs was delivered on budget and within pre-agreed timelines.

The result

In conjunction with third party vendors, Almac has successfully delivered a minitablet in stickpack sachet paediatric formulation for a first in class product with a robust manufacturing process suitable for routine commercial manufacture.

We can support your oral solid dose product development programme through experience, expertise and efficiency.



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