Evaluation of a Quality by Design (QbD) Approach for Process Development and Scale-Up of a Novel ALS Drug Product

David Ma MBA., Shawn McConnell, Sanjay Konagurthu Ph.D., Thermo Fisher Scientific
d.ma@thermofisher.com | shawn.mcconnell@thermofisher.com | sanjay.konagurthu@thermofisher.com
Joshua Cohen, Justin Klee, Amylyx Pharmaceuticals, Cambridge, MA, United States

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PURPOSE

AMX0035 is a potentially beneficial new treatment for people with amyotrophic lateral sclerosis (**ALS**). The purpose of the study is to discuss a Quality by Design (**QbD**) approach for process development and scale-up to commercial batches. Thermo Fisher's QbD methodology uses a step-wise approach consistent with ICH Q8 (R2) and associated regulatory guidelines to build quality into the drug product.

OBJECTIVE

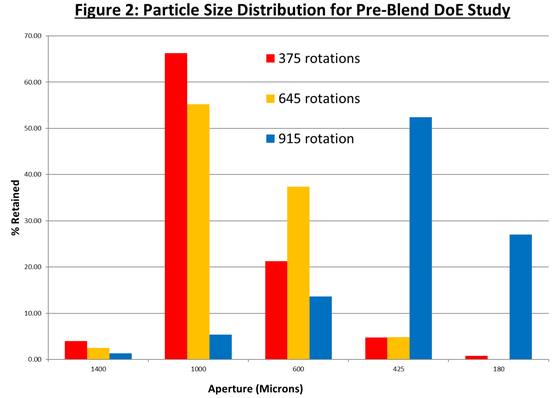
The primary objective of the QbD program is to establish a thorough knowledge base and understanding of the AMX-0035 Powder Blend product and dynamic relationship to the Quality Target Product Profile (**QTPP**). The program is designed to establish the risk levels, optimal design space and control strategy to consistently manufacture the drug product in accordance to all defined limits and quality specifications.

RESULTS

Pre-Blending DoE Study

No statistical significance found for Blend uniformity, dissolution and reconstitution times for all three batches. Significant differences was observed in the Particle size distribution (PSD) for all three batches after the pre-blending stage. In Figure 2, the pre-blend PSD shows **coarser** fraction of materials with shorter mixing time.

Figure 2: Particle Size Distribution for Pre-Blend DoE Study



Compaction DoE Study

In order to meet downstream packaging requirements, the physical characteristics of the final blend are **important** and thus a homogeneous particle size distribution is recommended. Thus, in order to achieve unimodal distribution, a pre-defined response targets in Table 4 was selected for the statistical model.

Table 4: Response Target for Statistical Model

Response	Target
Particle Size Distribution	
Material > 1400 µm	NMT 10 %
425 µm < Material < 1400 µm	45 % ≤ Material ≤ 65 %
Material < 425 µm	NMT 45 %
Reconstitution Time	NMT 15 minutes (alert limit)
TUDCA Dissolution	Q = 75 % → individual values NLT 85 % @15 minutes
PBA Dissolution	Q = 75 % → individual values NLT 85 % @ 15 minutes

Table 5: Optimal Compaction Parameters

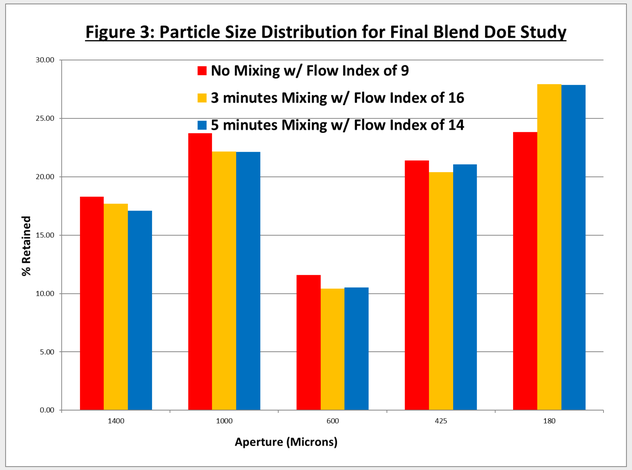
The optimal compaction parameters from the predicted model is shown in Table 5.

Input Factor	Value
Press Force	10.0 kN/cm
Gap Width	2.5 mm
Screen Size	1.5 mm

Final Blending DoE Study

Based on the analysis, no statistical significance was found for blend uniformity, reconstitution time and dissolution with regards to different mixing times. In Figure 3, differences were observed in the flow index for different mixing times. The blending duration at this stage of the manufacturing process could affect the final flow properties of the bulk material which is **critical** to minimizing weight variation in downstream packaging activities.

Figure 3: Particle Size Distribution for Final Blend DoE Study



METHODS

In the case of AMX-0035, the dosage form is a powder-in-a-sachet formulation intended to be delivered as a suspension in a liquid. A three phase step-wise approach is used to investigate the different stages in the manufacturing process. Figure 1 outlines the overall QbD design for AMX-0035 Powder Blend. Blend uniformity, physical characterization, dissolution and reconstitution time will be the **response factors** for the QbD program.

Table 1 outline the Pre-Blend DoE study that evaluates three different mixing durations. Compaction DoE study evaluates three different factors, Compaction Force, Compaction Gap and Screen Size at two different levels that is outlined in Table 2. Table 3 illustrates the Final Blending DoE study that evaluates three different mixing durations.

Figure 1: Overall QbD Process Flow Diagram

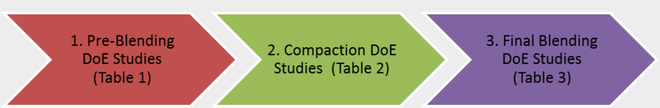


Table 1: Outline of Pre-blending DoE

Batch# (Description)	Number of revolutions
#1 (shortest mixing)	375 revolutions
#2 (target mixing)	645 revolutions
#3 (longest mixing)	915 revolutions

Table 2: Outline for Compaction DoE

Setting	Compaction Force (kN/ cm)	Compaction Gap (mm)	Screen Size (mm)
High	+1	+1	+1
Center	0	0	0
Low	-1	-1	-1

Table 3: Outline of Final Blending DoE

Batch# (Description)	Number of revolutions
#1 (No Mixing)	0 revolutions
#2 (Target Mixing)	61.5 revolutions
#3 (Extended Mixing)	102.5 revolutions

CONCLUSIONS

- The pre-blending DoE study suggests reduced mixing time can still yield desired CQAs under the conditions evaluated.
- With pre-defined response targets for physical properties, reconstitution time and dissolution, a statistical model was used to determine the optimal compaction parameters.
- The final blending DoE study suggests blending is not mandatory as CQAs were met after compaction.
- This program has identified a process space for pre-blending, compaction and final blending.

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