Overcoming Analytical Sample Preparation Issues to Improve Method Reliability

Challenge

Low out of specification assay results were being generated for a capsule-based pharmaceutical product, with significant cost implications for any batch wrongly rejected. Initial investigations by the analytical team pointed towards the sample preparation process as a source of variability.

Approach

A Britest study was carried out, to create a shared view of the issue that the team was trying to understand, and then to visualise and troubleshoot the sample preparation regime. The study, which involved all the analysts responsible for carrying out the procedure, broke the process down into fourteen unit operations, enabling twenty-seven potential sources of error / operator variation to be identified. Seven of these were prioritised for further investigation in a factorial experimental design.

The experiment established that overfilling sample flasks prior to mechanical shaking resulted in reduced agitation efficiency and consequently lower assay results. If agitation efficiency was compromised in this way the problem was exacerbated by reducing the extraction time prior to shaking, and when the capsules had been subjected to low humidity and temperature.

The team found however that by applying tighter controls to the pre-shake fill volume, sufficient extraction could be achieved irrespective of extraction time or capsule storage condition. A precision to tolerance ratio of 42% was achieved when fill volume was controlled to between 60% and 80% of flask capacity (<50% is indicative of a well controlled method).

Benefits

- Re-wording the test method procedure to restrict the fill volume to 60-75% of flask capacity restored the method to control, saving $10-50k per out of specification result.

Key Features:

Client - AstraZeneca

Industry - Application Area

Pharmaceuticals - Analytical method improvement

Challenge

Low out of specification assay results were being generated for a capsule-based pharmaceutical product. Initial investigations pointed towards sample preparation as a source of variability.

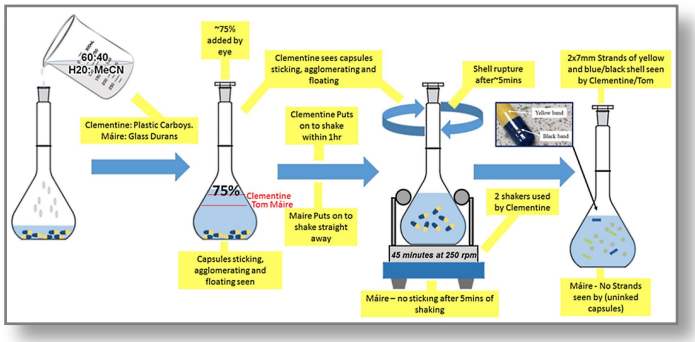
Solution

Britest tools were used to visualise the sample preparation regime in detail, breaking it down to identify potential sources of variation, and prioritise these for further investigation in a factorial experimental design.

Outcomes

The study established that by applying tighter controls to the volume of extractant solvent added prior to mechanical shaking, sufficient extraction could be achieved irrespective of other variations in sample history shown to be statistically significant.

Re-wording the test method restored the method to control, saving $10-50k per out of specification result prevented.



A Britest Rich Cartoon series helped identify subtle procedural variations and captured valuable operator observation and insight

We didn't have a lot of time to theorise. Visualising the method in operation enabled us to problem solve rapidly and effectively.

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Supporting organisations in gaining value from process understanding

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