

Specification setting with pharma customers

DFE pharma perspective

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Specification setting general considerations

Goal: To agree between supplier and customer exactly what the customer needs, within the possible product/process boundaries.

Regulators may also be considered customers

Hierarchy of specification setting

1. Pharmacopoeia requirement
2. Prescribed by the customer (potential FRC/CMA's)
3. Agreed with the customer

Requirements

1. Specification must match our process capability.
2. Analytical methods are either prescribed and performed per pharmacopoeia or are validated by our QC

Particle size characterization

Status Quo: Traditional method for establishing information on the PSD- in the Pharmaceutical industry- is still analytical sieving

Approach

1. If the PSD parameters are application critical: (E.g. Excipient grade used as filler, carrier or diluent)
 - 2 sided- PSD specifications; at least 3 points on the PSD specified (e.g. d_{10} , d_{50} and d_{90})
 - Uniformity of 'd' and 'x' nomenclature as described by ISO, meaning both can be used interchangeable.
 - More preferably a Particle size distribution measurement like laser diffraction.
 - Specifications are set by statistical analyses of the Process capability; during two years- twice every season
 - Morphology is not taken into account
2. If the PSD parameters are not critical: (E.g. Excipient grade that is dissolved)
 - 1 sided PSD specification is sufficient
 - Preference for laser diffraction since it is an easier method
 - Specification is e.g. determined by solubility rate of largest particles

Bulk Density

Bulk and tapped density method is prescribed in the pharmacopoeia e.g. USP <616>.

Methods employed by us:

Jolting volumeter – bulk and tapped density – the 'golden' standard in our industry

Scott volumeter- bulk density only

Density is -in our processes- measured to control:

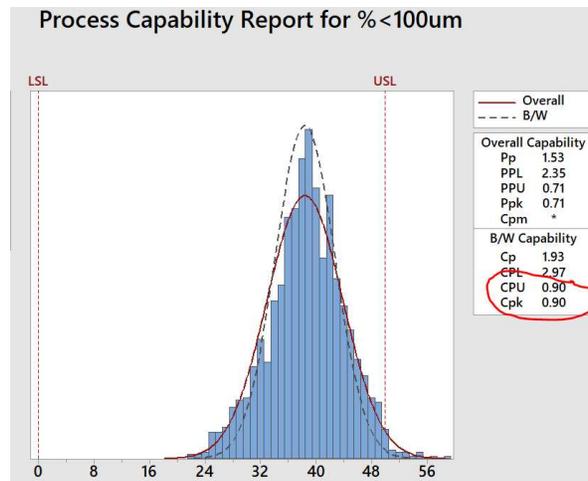
1. **Chemistry:** Bulk density describes particle internal structure like
extend of hydrolysis in Cellulose, Amorphous/crystalline ratio or extend of gelatinization of starches
2. **Porosity:** Reduce percolation (segregation).
3. **Flowability:** Ensure the product easily flows into the tablet die .

The specification limits are partly compendial prescribed and partly functionality determining. In case the limits are not prescribed- Specification setting is based on Process capability.

Specification setting based on process capability; practical example

Context: Customer dissolves the product

Issue: Old particle size specification: 50%<100 μ m (Alpine airjet sieve) lead to ~2x year Out of spec



Outcome: Agreed on new spec with customer that is better matching our capability (56%<100 μ m)

This is possible if the particle size is not a Functionality related Characteristic and not other users are using the product (rare).