Guidance Number: 043

Table 1: Typical potential critical process parameters

Process Step	Equipment Type (Examples)	Potential Critical Process Parameters[a]	Potential Critical Attributes
Milling (particle size reduction)- Ref (2)	Oscillator (Frewitt)	• Impeller used & RPM • Screen size • Pressure • Temperature • Position- knives/hammer • Feeder speed • Gap for impeller	• Bulk density • Particle size distribution • De-agglomeration
	Screening mills/Cone mill (e.g. Comil)		
	Impact/Hammer mill (e.g., Frewitt, Fitzpatrick)		
	Separators (e.g. Russell Finex, Sweco)	• Vibrations setting • Screen size • Feeder speed	
Mixing- Convection[a] (low shear; No homogenization required)	Anchor/Sweep (e.g., Ross, FrymaKoruma, Lee, GEI, Waukesha Cherry)	• Mixing time • Type Blades, Sweep • Blade position • Anchor Speed • Pumping characteristics • Jacket (temperatures/heat transfer properties) • Heating and cooling rates • Temperature uniformity • Congealing temp/rate • Vacuum (if applicable) • Tank/kettle shape (e.g. bottom) • Order and method of addition	• Homogeneity, potency (active, preservative) • Viscosity • Density or specific volume • Appearance • Microbial quality (microbial limits, sterility, as applicable)
	Panetary Mixer (AMF, Hobart, Littleford Day)	• Mixing time • Type Blades • Mixer Speed • Order of addition • Similar to Anchor/sweep	
	Impeller (Lightnin, Ross)	• Mixing time • Type, angle, location of Blade • Mixer Speed • Order/Rate of addition- (Vortex) • Similar to Anchor/Sweep	

Process Step	Equipment Type (Examples)	Potential Critical Process Parameters[a]	Potential Critical Attributes

Mixing- Convection (High Shear)	Dispersator (e.g., Lightnin, Ross, Gate)	• Impeller mixing time
		• Impeller Speed
		• Chopper mixing time and speed
		• Order of addition
			• Same as for High shear:
			  • Homogeneity, potency (active, preservative)
			  • Viscosity
			  • Density or specific volume
			  • Appearance
			  • Microbial quality (microbial limits, sterility, as applicable)
			
			Others more probable for high shear mixing:
			• Particle size distribution
			• pH (if applicable)

	Rotor Stator (Arde-Barinco, Fryma, Silverson)	• Design and size of rotor-stator (generator) • Rotor tip speed • Initial size of sample • Viscosity of medium • Time of processing or flow rate • Heating and cooling rates • Temperature uniformity • Volume of medium and concentration of sample • Shape of vessel and positioning of rotor-stator	
Mixing- Roller	Roller Mills (Ross, Stokes Merrill)	• Gap settings • Rollers speeds • Grooves (sizes), if applicable	• Viscosity • Density • Drug uniformity • Same as other mixers
Emulsification/ Homogenization	Low Shear (Lightnin, Moorhouse-Cowles, PRO scientific)	• Mixer/blade speed • Blade configuration • Location, pitch • Order of addition	• Drug Uniformity • Viscosity • Aeration • Density or specific gravity • Appearance • pH (if applicable, phases) • Firmness (Penetrometer) • Particle size distribution (for dispersions) • Sedimentation rate or volume • Drug release/dissolution (if applicable)
	High Shear (Dispersator, Rotor stator, Lightning, Niro, Romaco, Silverson)	• Pressure • Temperature • Number of passes • Valve and impingement design • Flow rate	
Deaeration	Off-line (batch) or In-line (Jaygo, Fryma, Lee, Mueller)	• Vacuum setting • Throughput • Recirculation	• Density or specific gravity • Viscosity • Phase stability

Process Step	Equipment Type (Examples)	Potential Critical Process Parameters[a]	Potential Critical Attributes
Transfer/Holding	Low Shear (gravity, peristaltic, screw, diaphragm) High Shear (centrifugal, piston, rotating gear)	• Flow rate • Agitation speeds • Type and size of tube or pipe • Temperatures • Protection from environment (e.g. cover, plastic)	• Viscosity • Density or specific gravity • Phase stability • Pourability • Resuspendability • Uniformity • Drug release/dissolution (if applicable)

Filling	Auger, Gear, Peristaltic, Piston (e.g.cream filling)	• Filling equipment parameters
		  • Speed
		  • Volume or weight
		  • Nozzle size
		• Hopper (stirring speed, heat, evaporation)
		• Filtration type/parameters
		• Inert gas (before/after)
		• Tube loading (manual vs. automatic)
		• Tube cleaning (compressed air, vacuum)
		• Embossing (tube)
		• Temperatures
			• Fill weight variation
			• Content uniformity
			• Assay/Degradation
			• Visual inspection
			• Viscosity
			• Density/Specific gravity
			• Fill accuracy (% from target) and fill precision (%RSD, CP, CPK)
			• Minimum fill
			• Drug release (in vitro) /dissolution (if applicable)
			• Other (e.g. metal particles for ophthalmics, gel strength)
			• Microbial (if applicable)

Sealers (capping, cutting)	Romaco (Unipac), M& O Perry, Kaps-All, Auto-Mate Tech.	• Speed • Temperature (heat seal) • Head or Seal pressure , (crimp/torquing) • Electromagnetic (induction) • Applied force (capping torque)	• Removal torque • Leakage/integrity • Eveness (of cut)

[a] Parameter of holding time (in-process material) is common to all unit process steps.