# SUPAC: Manufacturing Equipment Addendum Guidance for Industry

U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER)

> December 2014 Pharmaceutical Quality/CMC

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# **Guidance for Industry<sup>1</sup> SUPAC: Manufacturing Equipment Addendum**

This guidance represents the Food and Drug Administration's (FDA's or Agency's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance using the contact information on the title page of this guidance.

#### I. INTRODUCTION

17 This guidance combines and supersedes the following scale-up and post-approval changes

- 18 (SUPAC) guidances for industry: (1) SUPAC-IR/MR: Immediate Release and Modified
- 19 Release Solid Oral Dosage Forms, Manufacturing Equipment Addendum, and (2) SUPAC-SS

20 Nonsterile Semisolid Dosage Forms, Manufacturing Equipment Addendum.<sup>2</sup> It removes the lists

of manufacturing equipment that were in both guidances and clarifies the types of processes beingreferenced.

23

A draft guidance, *SUPAC: Manufacturing Equipment Addendum*, was published on April 1, 2013.
 Comments were received and changes were made to address those comments.

26

27 This SUPAC addendum should be used in conjunction with the following SUPAC guidances for

28 industry:<sup>3</sup> (1) Immediate Release Solid Oral Dosage Forms — Scale-Up and Post-Approval

29 Changes: Chemistry, Manufacturing and Controls, In Vitro Dissolution Testing, and In Vivo

30 Bioequivalence Documentation, (2) SUPAC-MR: Modified Release Solid Oral Dosage Forms

31 Scale-Up and Post-Approval Changes: Chemistry, Manufacturing and Controls; In Vitro

32 Dissolution Testing and In Vivo Bioequivalence Documentation, and (3) SUPAC-SS: Nonsterile

33 Semisolid Dosage Forms, Scale-Up and Post Approval Changes: Chemistry Manufacturing and

34 *Controls; In Vitro Release Testing and In Vivo Bioequivalence Documentation.*<sup>4</sup>

35

36 The SUPAC guidances define: (1) levels of chemistry, manufacturing, and control change; (2)

- 37 recommended chemistry, manufacturing, and controls tests for each level of change; (3)
- 38 recommended in vitro dissolution and release tests and/or in vivo bioequivalence tests for each

<sup>&</sup>lt;sup>1</sup> This guidance has been prepared by the Office of Pharmaceutical Science in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

 $<sup>^{2}</sup>$  For this guidance only, the new document that is a combination of these two guidances will be referred to as the *SUPAC addendum*.

<sup>&</sup>lt;sup>3</sup> We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

<sup>&</sup>lt;sup>4</sup> For this guidance only, this collective group of guidances will be referred to as *SUPAC guidances*.

- 39 level of change; and (4) recommended documentation that should support the change for new
- 40 drug applications and abbreviated new drug applications.
- 41
- 42 This SUPAC addendum, together with the SUPAC guidances, is intended to help you, the
- 43 manufacturer, determine the documentation you should submit to FDA regarding manufacturing
- 44 equipment changes.
- 45
- 46 FDA's guidance documents, including this guidance, do not establish legally enforceable
- 47 responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should
- be viewed only as recommendations, unless specific regulatory or statutory requirements are
  cited. The use of the word *should* in Agency guidances means that something is suggested or
  recommended, but not required.
- 50 51

#### 52 II. BACKGROUND

53

54 When the SUPAC equipment addenda were published with tables referencing specific 55 equipment, the tables were misinterpreted as equipment required by FDA. FDA recognizes

56 that scientific innovation and technology advancement are commonplace and play a significant

57 role in pharmaceutical development, manufacturing, and quality assurance, and we are

57 role in pharmaceutical development, manufacturing, and quarty assurance, and we are 58 concerned that such a misunderstanding could discourage advancements in manufacturing

59 technologies. Therefore, this revised SUPAC addendum contains general information on

60 SUPAC equipment and no longer includes tables referencing specific equipment. This

61 guidance also includes changes to clarify the types of processes being referenced.

#### 63 III. DISCUSSION

64

62

65 The information in this guidance is presented in broad categories of unit operation. For immediate or modified release solid oral dosage forms, broad categories include blending and 66 67 mixing, drying, particle size reduction/separation, granulation, unit dosage, coating and printing, and soft gelatin capsule encapsulation. For nonsterile semisolid dosage forms, broad categories 68 69 include particle size reduction and/or separation, mixing, emulsification, deaeration, transfer, and 70 packaging. Definitions and classifications are provided. For each operation, equipment is 71 categorized by class (operating principle) and subclass (design characteristic). Examples of types 72 of equipment, but not specific brand information, are given within the subclasses.

73

74 When assessing manufacturing equipment changes from one class to another or from one

- subclass to another, you can follow a risk-based approach that includes a rationale and complies
- 76 with the regulations, including the CGMP regulations.<sup>5, 6</sup> We also recommend addressing the

impact on the product quality attributes of equipment variations (via process parameters) when
 designing and developing the manufacturing process.<sup>7</sup>

78 designing and 79

<sup>&</sup>lt;sup>5</sup> 21 CFR 314.70.

<sup>&</sup>lt;sup>6</sup> 21 CFR 210-211.

<sup>&</sup>lt;sup>7</sup> L. X. Yu, G. Amidon, M. A. Khan, S. W. Hoag, J. Polli, G. K. Raju, and J. Woodcock, Understanding Pharmaceutical Quality by Design. The AAPS Journal. March 2014.

When making equipment changes, you will need to determine the filing requirement.<sup>8</sup> The 80 81 SUPAC guidances provide information on how to do so. FDA will assess the changes based on 82 the types of equipment changes being considered. If you choose an approach that exceeds the 83 SUPAC guidances and addendum, FDA will assess the changes provided they are supported by 84 a suitable risk-based assessment. 85 86 At the time of the equipment change, you should have available the scientific data and rationale used to determine the type of change and documentation required. This information is subject to 87 88 FDA review at its discretion. 89 90 IV. SUPAC IR/MR INFORMATION 91 92 A. Particle Size Reduction/Separation 93 94 1. Definitions 95 96 a. Unit Operations 97 98 i. Particle Size Reduction: The mechanical process of breaking particles into 99 smaller pieces via one or more particle size reduction mechanisms. The mechanical process used generally is referred to as milling. 100 101 102 a. Particle – Refers to either a discrete particle or a grouping of particles, 103 generally known as an agglomerate. 104 105 b. Particle Size Reduction Mechanisms 106 107 • Impact - Particle size reduction by applying an 108 instantaneous force perpendicular to the particle/agglomerate surface. The force can result from 109 particle-to-particle or particle-to-mill surface collision. 110 111 112 Attrition - Particle size reduction by applying a force in a • 113 direction parallel to the particle surface. 114 115 Compression - Particle size reduction by applying a force 116 slowly (as compared to Impact) to the particle surface in a direction toward the center of the particle. 117 118 119 Cutting - Particle size reduction by applying a • 120 shearing force to a material. 121 122 Particle Separation: Particle size classification according to particle size ii. 123 alone. 124

125	b. C	perating Principles
126		
127	i	Fluid Energy Milling
128		
129		Particles are reduced in size as a result of high-speed particle-to-particle
130		impact and/or attrition; also known as micronizing.
130		impact and of author, also known as incromenig.
131	ii	. Impact Milling
	11	. Impact winning
133		
134		Particles are reduced in size by high-speed mechanical impact or impact
135		with other particles; also known as milling, pulverizing, or comminuting.
136		
137	iii	. Cutting
138		
139		Particles are reduced in size by mechanical shearing.
140		
141	iv	. Compression Milling
142		
143		Particles are reduced in size by compression stress and shear between
144		two surfaces.
145		two surfaces.
145		Sorooning
140 147	v	Screening
147		Particles are reduced in size by mechanically induced attrition through a
148		
		screen. This process commonly is referred to as milling or
150		deagglomeration.
151		Tymhla Milling
152	V1	. Tumble Milling
153		
154		Particles are reduced in size by attrition utilizing grinding media.
155		
156	V11	Separating
157		
158		Particles are segregated based upon particle size alone and without any
159		significant particle size reduction. This process commonly is referred to as
160		screening or bolting.
161		
162	2. Equipment C	Classifications
163		
164	a. Fluid	Energy Mills
165		
166	Fluid	energy mill subclasses have no moving parts and primarily are distinguished
167		one another by the configuration and/or shape of their chambers, nozzles,
168		lassifiers.
169		
170	• Т	angential Jet
170		oop/Oval
1/1	▼ L	00p/0vai

172	Opposed Jet
173	Opposed Jet with Dynamic Classifier
174	Fluidized Bed
175	• Fixed Target
176	Moving Target
177	High Pressure Homogenizer
178	
179	b. Impact Mills
180	I
181	Impact mill subclasses primarily are distinguished from one another by the
182	configuration of the grinding heads, chamber grinding liners (if any), and
183	classifiers.
184	
185	Hammer Air Swept
186	Hammer Conventional
187	• Pin/Disc
188	• Cage
189	• Cage
190	c. Cutting Mills
191	
192	Although cutting mills may differ from one another in whether the knives are
193	movable or fixed and in the classifier configuration, no cutting mill subclasses
194	have been identified.
195	
196	d. Compression Mills
197	
198	Although compression mills may differ from one another in whether one or both
199	surfaces are moving, no compression mill subclasses have been identified.
200	
201	e. Screening Mills
202	
203	Screening mill subclasses primarily are distinguished from one another by the
204	rotating element.
205	
206	Rotating Impeller
207	Rotating Screen
208	Oscillating Bar
209	
210	f. Tumbling Mills
211	
212	Tumbling mill subclasses primarily are distinguished from one another by the
213	grinding media used and by whether the mill is vibrated.
214	
215	Ball Media
216	Rod Media
217	Vibrating

218					
219		g.	Separators		
220		-	-		
221			Separator subclasses primarily are distinguished from one another by the		
222			mechanical means used to induce particle movement.		
223					
224			• Vibratory	/Shaker	
225			• Centrifuga		
226			U		
227		B.	Blending and	l Mixing	
228					
229	1.	Definit	tions		
230		- <b>J</b>			
231		a.	Unit Operatio	ns	
232			I		
233			Blending and	Mixing: The reorientation of particles relative to one another in	
234			0	ve uniformity.	
235					
236		b.	Operating Pri	nciples	
237		0.	operating I II	norpros	
238			i.	Diffusion Blending (Tumble)	
239			1.	Diffusion Dichang (Tumolo)	
240				Particles are reoriented in relation to one another when they are	
241				placed in random motion and interparticular friction is reduced	
242				as the result of bed expansion (usually within a rotating	
242				container); also known as tumble blending.	
243 244				container), also known as tumble blending.	
244 245			ii.	Convection Mixing	
			11.		
246 247				Douticles are requirered in relation to one another as a result	
247 248				Particles are reoriented in relation to one another as a result of machanical maximum as models or plays	
				of mechanical movement; also known as paddle or plow	
249				mixing.	
250					
251			iii.	Pneumatic Mixing	
252					
253				Particles are reoriented in relation to one another as a result of	
254				the expansion of a powder bed by gas.	
255					
256	2.	Equipr	nent Classifica	tions	
257					
258		a.	Diffusion Mix	ters (Tumble)	
259					
260				er subclasses primarily are distinguished by geometric shape and	
261			the positionin	g of the axis of rotation.	
262					
263			• V-blender	S	
264			• Double Co	one Blenders	

265			Slant Cone Blenders
266			Cube Blenders
267			• Bin Blenders
268			Horizontal/Vertical/Drum Blenders
269			Static Continuous Blenders
270			Dynamic Continuous Blenders
271			
272		b.	Convection Mixers
273			
274			Convection blender subclasses primarily are distinguished by vessel shape and
275			impeller geometry.
276			
277			Ribbon Blenders
278			Orbiting Screw Blenders
279			Planetary Blenders
280			• Forberg Blenders
281			Horizontal Double Arm Blenders
282			Horizontal High Intensity Mixers
283			<ul> <li>Vertical High Intensity Mixers</li> </ul>
283			<ul> <li>Diffusion Mixers (Tumble) with Intensifier/Agitator</li> </ul>
285			• Diffusion wixers (Tumole) with intensitien/Agitator
285		с.	Pneumatic Mixers
287		с.	Theumatic withers
287			Although pneumatic mixers may differ from one another in vessel geometry, air
289			nozzle type, and air nozzle configuration, no pneumatic mixer subclasses have
290			been identified.
290 291			been identified.
292			
292		C.	Granulation
294		с.	Of unfunction
295	1.	Defini	tions
296			
297		a.	Unit Operations
298			1
299			Granulation: The process of creating granules. The powder morphology is
300			modified through the use of either a liquid that causes particles to bind through
301			capillary forces or dry compaction forces. The process will result in one or more
302			of the following powder properties: enhanced flow; increased compressibility;
303			densification; alteration of physical appearance to more spherical, uniform, or
304			larger particles; and/or enhanced hydrophilic surface properties.
305			
306		b.	Operating Principles
307			
308			i. Dry Granulation
309			- -

310 311		Dry powder densification and/or agglomeration by direct physical compaction.
312 313	ii.	Wet High-Shear Granulation
314		
315		Powder densification and/or agglomeration by the incorporation
316		of a granulation fluid into the powder with high-power-per-unit
317		mass, through rotating high-shear forces.
318		muss, unough rotating ingh shear rorees.
319	iii.	Wet Low-Shear Granulation
320	111.	
321		Powder densification and/or agglomeration by the incorporation
322		of a granulation fluid into the powder with low-power-per-unit
323		mass, through rotating low-shear forces.
		mass, unough folding low-shear forces.
324 325	iv.	Low-Shear Tumble Granulation
326	1V.	Low-shear runnole Granulation
320 327		Pour densification and/or agalemention by the incorporation
328		Powder densification and/or agglomeration by the incorporation
		of a granulation fluid into the powder with low-power-per-unit
329		mass, through rotation of the container vessel and/or intensifier
330		bar.
331		Entrucion Computation
332	V.	Extrusion Granulation
333		
334		Plasticization of solids or wetted mass of solids and
335		granulation fluid with linear shear through a sized orifice using
336		a pressure gradient.
337		
338	vi.	Rotary Granulation
339		
340		Spheronization, agglomeration, and/or densification of a wetted or
341		non-wetted powder or extruded material. This is accomplished by
342		centrifugal or rotational forces from a central rotating disk, rotating
343		walls, or both. The process may include the incorporation and/or
344		drying of a granulation fluid.
345		
346	vii.	Fluid Bed Granulation
347		
348		Powder densification and/or agglomeration with little or no shear
349		by direct granulation fluid atomization and impingement on
350		solids, while suspended by a controlled gas stream, with
351		simultaneous drying.
352		
353	viii.	Spray Dry Granulation
354		

355 356 357		A pumpable granulating liquid containing solids (in solution or suspension) is atomized in a drying chamber and rapidly dried by a controlled gas stream, producing a dry powder.
358 359	ix.	Hot-melt Granulation
3 <i>5</i> 9 360	1X.	not-ment Granulation
360 361		An agglomeration process that utilizes a molten liquid as a
362		binder(s) or granulation matrix in which the active
363		pharmaceutical ingredient (API) is mixed and then cooled down
364		followed by milling into powder. This is usually accomplished
365		in a temperature controlled jacketed high shear granulating tank
366		or using a heated nozzle that sprays the molten binders(s) onto
367		the fluidizing bed of the API and other inactive ingredients.
368		the function of the first function inderive ingredients.
369	Х.	Melt Extrusion
370	<b>A</b> •	
371		A process that involves melting and mixing API and an excipient
372		(generally a polymer) using low or high shear kneading screws
373		followed by cooling and then milling into granules. Thermal
374		energy for melting is usually supplied by the electric/water heater
375		placed on the barrel. Materials are either premixed or fed into an
376		extruder separately. Melt extruder subclasses primarily are
377		distinguished by the configuration of the screw.
378		
379		• Single screw extruder
380		• Twin screw extruder
381		
382	2. Equipment Classifica	tion
383 384	a. Dry Granulate	)r
385	a. Dry Grandiau	
386	Dry granulato	r subclasses primarily are distinguished by the densification force
387	application me	
388	upprication in	
389	• Slugging	
390	<ul><li>Roller Con</li></ul>	maction
391		npaction
392	b. Wet High-She	ear Granulator
393	0. Wet High-Sh	
394	Wet high-she	r granulator subclasses primarily are distinguished by the
395	-	itioning of the primary impellers; impellers can be top, bottom,
396	or side driven	
397		
398	• Vertical (	Γop or Bottom Driven)
399	,	l (Side Driven)
400	• 11011201114	

401 402	c. Wet Low-Shear Granulator
403 404 405 406	Wet low-shear granulator subclasses primarily are distinguished by the geometry and design of the shear inducing components; shear can be induced by rotating impeller, reciprocal kneading action, or convection screw action.
407	• Planetary
408	• Kneading
409	• Screw
410	
411	d. Low-Shear Tumble Granulator
412	
413	Although low-shear tumble granulators may differ from one another in vessel
414	geometry and type of dispersion or intensifier bar, no low-shear tumble
415	granulator subclasses have been identified.
416	
417	• Slant cone
418	• Double cone
419	• V-blender
420 421	e. Extrusion Granulator
421	e. Extrusion Granulator
422	Extrusion granulator subclasses primarily are distinguished by the
424	orientation of extrusion surfaces and driving pressure production
425	mechanism.
426	
427	Radial or Basket
428	Axial
429	• Ram
430	Roller, Gear, or Pelletizer
431	
432	f. Rotary Granulator
433	
434	Rotary granulator subclasses primarily are distinguished by their structural
435	architecture. They have either open top architecture, such as a vertical centrifugal
436	spheronizer, or closed top architecture, such as a closed top fluid bed dryer.
437	
438	• Open
439	• Closed
440	
441	g. Fluid Bed Granulator
442	Although fluid had granulators may differ from one spather in accountry
443 444	Although fluid bed granulators may differ from one another in geometry, operating pressures, and other conditions, no fluid bed granulator subclasses
444	have been identified.
446	have been denumed.
טדו	

447	h.	Spray Dry Gr	anulator		
448					
449			ay dry granulators may differ from one another in geometry,		
450		1 01	operating pressures, and other conditions, no spray dry granulator subclasses have		
451		been identified.			
452					
453	i.	Hot-melt Gra	nulator		
454					
455		•	t-melt granulator may differ from one another in primarily melting the		
456			dient (particularly the binder or other polymeric matrices), no		
457		subclasses ha	ve been identified at this time.		
458					
459	Note:				
460	0 1	1 1	ent is capable of performing multiple discrete unit operations (mixing,		
461	0 0		it was evaluated solely for its ability to granulate. If multifunctional		
462 463	integrated un	-	crete steps (fluid bed granulator/drier), the unit was evaluated as an		
403 464	integrated u	III.			
465	D.	Drying			
466					
467	1. Defini	tions			
468					
469	a.	Unit Operation	on		
470		~			
471		Drying: The	removal of a liquid from a solid by evaporation.		
472 473	h	On anotin a Dri	noinlos		
473 474	0.	Operating Pri	liciples		
475		i.	Direct Heating, Static Solids Bed		
476		1.	Direct ficaling, static solids bed		
477			Heat transfer is accomplished by direct contact between the wet		
478			solids and hot gases. The vaporized liquid is carried away by the		
479			drying gases. There is no relative motion among solid particles.		
480			The solids bed exists as a dense bed, with the particles resting upon		
481			one another.		
482					
483		ii.	Direct Heating, Moving Solids Bed		
484					
485			Heat transfer is accomplished by direct contact between the wet		
486			solids and hot gases. The vaporized liquid is carried away by the		
487			drying gases. Solids motion is achieved by either mechanical		
488			agitation or gravity force, which slightly expands the bed enough to		
489			flow one particle over another.		
490 401		:::	Direct Hesting Eluidized Solids Ded		
491		iii.	Direct Heating, Fluidized Solids Bed		
492					

493 494 495 496 497 498 499	Heat transfer is accomplished by direct contact between the wet solids and hot gases. The vaporized liquid is carried away by the drying gases. The solids are in an expanded condition, with the particles supported by drag forces caused by the gas phase. The solids and gases intermix and behave like a boiling liquid. This process commonly is referred to as fluid bed drying.
500 iv.	Direct Heating, Dilute Solids Bed, Spray Drying
501 502 503	Heat transfer is accomplished by direct contact between a highly dispersed liquid and hot gases. The feed liquid may be a solution,
504 505 506 507 508 509	slurry, emulsion, gel or paste, provided it is pumpable and capable of being atomized. The fluid is dispersed as fine droplets into a moving stream of hot gases, where they evaporate rapidly before reaching the wall of the drying chamber. The vaporized liquid is carried away by the drying gases. The solids are fully expanded and so widely separated that they exert essentially no influence on
510 511	one another.
512 v.	Direct Heating, Dilute Solids Bed, Flash Drying
513	
514	Heat transfer is accomplished by direct contact between wet solids
515	and hot gases. The solid mass is suspended in a finely divided state
516 517	in a high-velocity and high-temperature gas stream. The vaporized liquid is carried away by the drying gases.
518	nquia is carried a way by the drying gases.
	Indirect Conduction Moving Solids Rod
	Indirect Conduction, Moving Solids Bed
520	
521	Heat transfer to the wet solid is through a retaining wall. The
522 522	vaporized liquid is removed independently from the heating
523 524	medium. Solids motion is achieved by either mechanical agitation or gravity force, which slightly expands the bed enough to flow one
525	particle over another.
526	L
527 vii.	Indirect Conduction, Static Solids Bed
528	
529	Heat transfer to the wet solid is through a retaining wall. The
530	vaporized liquid is removed independently from the heating
531	medium. There is no relative motion among solid particles. The
532	solids bed exists as a dense bed, with the particles resting upon one
533	another.
534	
535 viii.	Indirect Conduction, Lyophilization
536	
537	Drying in which the water vapor sublimes from the product after
538	freezing.

539				
540			ix.	Gas Stripping
541				
542				Heat transfer is a combination of direct and indirect heating. The
543				solids motion is achieved by agitation and the bed is partially
544				fluidized.
545				
546			х.	Indirect Radiant, Moving Solids Bed
547				
548				Heat transfer is accomplished with varying wavelengths of energy.
549				Vaporized liquid is removed independently from the solids bed.
550				The solids motion is achieved by mechanical agitation, which
551				slightly expands the bed enough to flow one particle over one
552				another. This process commonly is referred to as microwave
553				drying.
554				
555	2.	Equipr	nent Classifica	tions
556			, , , , , , , , , , , , , , , , , , ,	
557		a.	Direct Heating	g, Static Solids Bed
558			_	
559			Static solids be	ed subclasses primarily are distinguished by the method of
560			moving the so	lids into the dryer.
561				
562			• Tray and T	Fruck
563			• Belt	
564				
565		b.	Direct Heating	, Moving Solids Bed
566			-	
567			Moving solids	bed subclasses primarily are distinguished by the method or
568			technology for	moving the solids bed.
569				
570			• Rotating T	ray
571			Horizontal	Vibrating Conveyor
572				
573		с.	Direct Heating	, Fluidized Solids Bed (Fluid Bed Dryer)
574			-	
575			Although fluid	l bed dryers may differ from one another in geometry, operating
576			pressures, and	other conditions, no fluidized solids bed dryer subclasses have
577			been identified	l.
578				
579		d.	Direct Heating	g, Dilute Solids Bed, Spray Dryer
580				
581			Although spra	y dryers may differ from one another in geometry, operating
582			pressures, and	other conditions, no spray dryer subclasses have been identified.
583				

584	e.	Direct Heating, Dilute Solids Bed, Flash Dryer
585		
586		Although flash dryers may differ from one another in geometry, operating
587		pressures, and other conditions, no flash dryer subclasses have been identified.
588		
	£	Indirect Conduction Hosting Maring Solids Ded
589	f.	Indirect Conduction Heating, Moving Solids Bed
590		
591		Moving solids bed subclasses primarily are distinguished by the method or
592		technology for moving the solids bed.
593		
594		• Paddle
595		<ul><li>Rotary (Tumble)</li></ul>
596		Agitation
597		
598	g.	Indirect Conduction Heating, Static Solids Beds
599		
600		No indirect heating, static solids bed shelf dryer subclasses have been
601		identified.
602		
	h	Indirect Conduction, Lyonhilization
603	11.	Indirect Conduction, Lyophilization
604		
605		No lyophilizer subclasses have been identified.
606		
607	i.	Gas Stripping
608		
609		Although gas stripping dryers may differ from one another in geometry, shape of
610		agitator, and how fluidizing gas is moved through the bed, no gas stripping dryer
611		subclasses have been identified.
		subclasses have been luchtmed.
612		
613	j.	Indirect Radiant Heating, Moving Solids Bed (Microwave Dryer)
614		
615		Although microwave dryers may differ from one another in vessel
616		geometry and the way microwaves are directed into the solids, no
617		indirect radiant heating, moving solids bed dryer subclasses have been
618		identified.
		identified.
619	NL-4 TC	
620		ingle piece of equipment is capable of performing multiple discrete unit operations
621	· · · ·	nulating, drying), the unit was evaluated solely for its ability to dry. The drying
622		vas sorted into similar classes of equipment, based upon the method of heat transfer
623	and the dyna	amics of the solids bed.
624		
625	Е.	Unit Dosing
626		
627	1. Defin	itions
628		
629	a.	Unit Operation
630	a.	Onit Operation
11211		

631			Unit Dosing:	The division of a powder blend into uniform single portions for
632			delivery to pa	tients.
633				
634		b.	Operating Print	nciples
635				
636			i.	Tabletting
637				
638				The division of a powder blend in which compression force is
639				applied to form a single unit dose.
640				
641			ii.	Encapsulating
642				
643				The division of material into a hard gelatin capsule. Encapsulators
644				should all have the following operating principles in common:
645				rectification (orientation of the hard gelatin capsules), separation of
646				capsule caps from bodies, dosing of fill material/formulation,
647				rejoining of caps and bodies, and ejection of filled capsules.
648				
649			iii.	Powder Filling
650				
651				The division of a powder blend into a container closure system.
652	2.	Eauin	nent Classifica	ations
653		Equip		
654		a.	Tablet Press	
655			1.00100111000	
656			Tablet press s	ubclasses primarily are distinguished from one another by the
657			-	he powder blend is delivered to the die cavity. Tablet presses can
658				ers without mechanical assistance (gravity), with mechanical
659			-	wer assisted), by rotational forces (centrifugal), and in two different
660				re a tablet core is formed and subsequently an outer layer of coating
661				plied (compression coating).
662			materiar is up	pried (compression couring).
663			• Gravity	
664			<ul><li>Oravity</li><li>Power As</li></ul>	sisted
665				
			Centrifuga	
666			• Compress	ion Coating
667			<b>T</b> 11 4	
668			1	ubclasses are also distinguished from one another for some special
669 670				ts where more than one hopper and precise powder feeding
670 671			mechanism m	hight be necessary.
671				
672				let press for micro/mini tablet
673			• Multi-laye	er tablet press (bi-layer, tri-layer)
674			_	
675		b.	Encapsulator	
676				

677		Encapsulator	subclasses primarily are distinguished from one another by the
678		method that i	s used for introducing material into the capsule. Encapsulators
679		can deliver m	naterials with a rotating auger, vacuum, vibration of perforated
680		plate, tampin	g into a bored disk (dosing disk), or cylindrical tubes fitted with
681		pistons (dosa	tor).
682		I `	
683		• Auger	
684		• Vacuum	
685		Vibratory	I
686		<ul> <li>Dosing D</li> </ul>	
687		<ul><li>Dosnig D</li><li>Dosator</li></ul>	715K
688		• Dosator	
689	c.	Powder Filler	r
690	C.	Towder Tille	
690 691		Subalassas of	f powder fillers primarily are distinguished by the method used to
692			redetermined amount for container fill.
693		denver the pr	edetermined amount for container fin.
		• Veen	
694		• Vacuum	
695 606		• Auger	
696 697	F.	Soft Colotin	Conculo
698	г.	Soft Gelatin	Capsule
699	1. Defini	tions	
700	1. Dejini		
700	a.	Unit Operation	one
701	u.	enit operativ	
702		i.	Gel Mass Preparation: The manufacture of a homogeneous,
704		1.	degassed liquid mass (solution) of gelatin, plasticizer, water, and
705			other additives, either in solution or suspension, such as colorants,
706			pigments, flavors, preservatives, etc., that comprise a unique
707			functional gel shell formation. The operation may be performed in
708			discreet steps or by continuous processing. Minor components can
709			be added after the liquid gel mass is made.
710			
711		ii.	Fill Mixing: The mixing of either liquids or solids with other liquids
712			to form a solution; blending of limited solubility solid(s) with a
713			liquid carrier and suspending agents used to stabilize the blend to
714			form a suspension; or the uniform combination of dry inert and drug
715			active substances to form a dry powder fill suitable for
716			encapsulation. The reader should refer to the other sections of this
717			document for dry fill manufacture.
718			
719		iii.	Encapsulation: The continuous casting of gel ribbons, with liquid
720			fill material being injected between the gel ribbons using a positive
721			displacement pump or, for dry materials being gravity or force fed
722			with capsule formation using a rotary die.
723			
123			

724 725 726 727 728		iv.	Washing: The continuous removal of a lubricant material from the outside of the formed capsule. The washing operation is unique to each manufacturer's operation and generally uses in-house fabricated equipment. This equipment will not be discussed in this guidance document.
729			
730		v.	Drying: The removal of the majority of water from the capsule's
731			gel shell by tumbling and subsequent tray drying using conditioned
732			air, which enhances the size, shape, and shell physical properties of
733			the final product. The drying operation is unique to each
734			manufacturer's operation and generally uses in-house fabricated
735			equipment. This equipment will not be discussed in this guidance
736			document.
737 738		:	Inspection (Sorting). The process wherein undesirchle concules are
739		vi.	Inspection/Sorting: The process wherein undesirable capsules are
739			removed, including misshapen, leaking, and unfilled capsules as well as agglomerates of capsules.
			wen as aggiomerates of capsules.
741		:	Divinting. The marking of a consult surface for the number of
742 743		vii.	Printing: The marking of a capsule surface for the purpose of
			product identification, using a suitable printing media or method.
744 745	h Onoro	tin a Duin	animlas
745	b. Opera	ung Fin	icipies
740		i.	Mixing
748		1.	winxing
749			The combination of solid and liquid components, including
750			suspending aid(s) at either ambient or elevated temperatures to
751			form a solution, suspension, or dry powder blend for the
752			manufacture of gel mass or fill material. Mixing also includes
753			the incorporation of minor components into the liquid gel mass.
754			the meorporation of minor components into the riquid ger mass.
755		ii.	Deaggregation
756		11.	Deaggregation
757			The removal of aggregates using a suitable homogenizer/mill to
758			provide a pumpable fill material. The procedure has minimal
759			effect on the particle size distribution of the initial solid
760			component(s), and is viewed as a processing aid. <sup>9</sup>
761			component(s), and is viewed as a processing and.
762		iii.	Deaeration
763			
764			The removal of entrapped air from either the gel mass or fill
765			material, solution or suspension. This process can take place in
766			either the mixing vessel, through the application of vacuum, or
767			a separate off-line step.
768			a separate on mie step.

<sup>&</sup>lt;sup>9</sup> Carstensen, J. T., Theory of Pharmaceutical Systems, Volume 11 Heterogeneous Systems, Academic Press, New York, NY, 1973, p 51.

769		iv.	Holding
770			The store of liquid cal mass on fill motorial in a massal with
771 772			The storage of liquid gel mass or fill material in a vessel, with a mixer or without, prior to encapsulation, which also may be
773			equipped with a jacket for either heating or cooling.
774			equipped with a jacket for ender nearing of cooning.
775		v.	Encapsulation
776			10
777			The formation of capsules using a rotary die machine. <sup>10</sup>
778			
779		vi.	Inspection/Sorting
780			
781			The physical removal of misshapen, leaking, or
782			agglomerated capsules, using either a manual or automatic
783			operation.
784 785		::	Drinting
785 786		vii.	Printing
780 787			The user of this document is asked to refer to the coating/printing
788			section, in which the use of various pieces of equipment are defined
789			and categorized.
790			
791	2. Equipment Cla	issifica	tions
792	1.1.1		
793	a. Mixers	and M	ixing Vessels
794			C
795	Mixer a	and mix	xing vessel subclasses primarily are distinguished by the mixing
796	energy	, mixer	type, and whether a jacketed vessel with vacuum capabilities is
797	used in	conjur	action with a specific mixer.
798			
799	• Lov	w Ener	gy Mixer
800	• Hig	gh Ener	gy Mixer
801		netary	
802	• Jac	keted V	Vessel With and Without Vacuum
803			
804	b. Deaggi	regator	S
805			
806		-	subclasses primarily are distinguished by the type of
807	mechar	ncal ac	tion imparted to the material.
808		how/0+	
809	• R0	tor/Sta	loi

<sup>&</sup>lt;sup>10</sup> Lachman, L., H. A. Lieberman, and J. L. Kanig (Eds.), The Theory and Practice of Industrial Pharmacy, Chapter 3, p. 359 (Stanley, J. P.), Philadelphia Lea & Febiger, 1971; Tyle, P. (Ed.), Specialized Drug Delivery Systems, Manufacturing and Production Technology, Chapter 10, p. 409 (Wilkinson, P.K. and F.S. Hom), New York; M. Dekker, 1990; Porter, S., Remington's Pharmaceutical Sciences, Edition 18, Chapter 89, pp. 1662 - 1665, Easton, Penn.: Mack Publishing Co.

810			• Roller
811			Cutting Mills
812			• Stone Mills
813			Tumbling Mills
814			
815		с.	Deaerators
816			
817			Deaerator subclasses primarily are distinguished by the air removal path, either
818			through the bulk or through a thin film, and whether it is a batch or in-line
819			process.
820			-
821			Vacuum Vessel
822			Off Line/In Line
823			
824		d.	Holding Vessels
825			
826			Although holding vessels may differ from one another, based upon whether they
827			are jacketed, with and without integrated mixing capabilities, no holding vessel
828			subclasses have been identified.
829			
830			• Jacketed vessel with and without mixing system
831			8.9.
832		e.	Encapsulators
833			
834			Encapsulator subclasses primarily are distinguished by the method used to inject
835			the fill material.
836			
837			Positive Displacement Pump
838			Gravity or Force Fed
839			
840		f.	Inspection/Sorting
841			
842			Inspection/sorting equipment subclasses primarily are distinguished by the
843			method used to present the capsule for viewing and mechanical method of
844			separation.
845			•
846			• Belt
847			Vibratory
848			• Roller
849			Rotary Table
850			Electromechanical
851			
852		G.	Coating/Printing/Drilling
853			······································
854	1.	Defini	itions
855		v	

856	a.	Unit O	peration	1	
857					
858			i.	Coating	g: The uniform deposition of a layer of material on
859				or arou	nd a solid dosage form, or component thereof, to:
860					
861				a.	Protect the drug from its surrounding environment
862					(air, moisture, and light), with a view to improving
863					stability.
864				b.	Mask unpleasant taste, odor, or color of the drug.
865				c.	Increase the ease of ingesting the product for the patient.
866					Impart a characteristic appearance to the tablets, which
867					facilitates product identification and aids patient
868					compliance.
869				e.	Provide physical protection to facilitate handling. This
870					includes minimizing dust generation in subsequent unit
871					operations.
872				f.	Reduce the risk of interaction between incompatible
873					components. This would be achieved by coating one or
874					more of the offending ingredients.
875				g.	Modify the release of drug from the dosage form. This
876					includes delaying, extending, and sustaining drug substance
877					release.
878				h.	Modify the dosage form by depositing the API or drug
879					substance on or around a core tablet, which could be a
880					placebo core tablet or a tablet containing another drug or a
881					fractional quantity of the same drug.
882					
883					ating material deposition typically is accomplished
884				through	n one of six major techniques:
885					
886				a.	Sugar Coating - Deposition of coating material onto
887					the substrate from aqueous solution/suspension of
888					coatings, based predominately upon sucrose as a raw
889					material.
890				b.	Film Coating - The deposition of polymeric film onto
891					the solid dosage form.
892				c.	Core Enrobing - The gelatin coating of gravity or force
893					fed pre- formed tablets or caplets.
894				d.	Microencapsulation - The deposition of a coating material
895					onto a particle, pellet, granule, or bead core. The
896					substrate in this application ranges in size from submicron
897					to several millimeters. It is this size range that
898					differentiates it from the standard coating described in 1
899					and 2 above.
900				e.	Compression Coating (also addressed in the Unit Dosing
901					section) - A coating process where a dry coatings blend is
902					applied on a previously compressed core tablet using a

903 904 905 906 907 908 909			<ul> <li>tablet compression machine.<sup>11</sup> Therefore, this process is also known as a dry coating process that does not involve any water or any other solvent in the coating process.</li> <li>f. Active/API coating - Deposition of active pharmaceutical ingredient (API or drug substance) on or around a core tablet utilizing any of the above five coating techniques.</li> </ul>
910 911		ii.	Printing: The marking of a capsule or tablet surface for the purpose of product identification. Printing may be accomplished
912			by either the application of a contrasting colored polymer (ink)
913			onto the surface of a capsule or tablet, or by the use of laser
914			etching.
915			
916			The method of application, provided the ink formulation is not
917			altered, is of no consequence to the physical-chemical properties of
918			the product.
919			
920		iii.	Drilling: The drilling or ablating of a hole or holes through the
921			polymeric film coating shell on the surfaces of a solid oral dosage
922			form using a laser. The polymeric film shell is not soluble in
923			vivo. The hole or holes allow for the modified release of the drug
924			from the core of the dosage form.
925			
926	b. Opera	ating Prin	nciples
927			
928		i.	Pan Coating
929			The uniform deposition of coating material onto the surface of a
930			solid dosage form, or component thereof, while being translated via
931			a rotating vessel.
932			
933		ii.	Gas Suspension
934			
935			The application of a coating material onto a solid dosage form, or
936			component thereof, while being entrained in a process gas stream.
937			
938			Alternatively, this may be accomplished simultaneously by
939			spraying the coating material and substrate into a process gas
940			stream.
941			
942		iii.	Vacuum Film Coating
943			

<sup>&</sup>lt;sup>11</sup> W.C. Gunsel & R.G. Dusel. Compression-coated and layer tablets. In H.A.Lieberman, L. Lachman & B. Schwartz (Eds), Pharmaceutical Dosage Forms: Tablets Vol 1, 1989, pp. 247-249. Mercel Dekker, Inc.

944 945 946					This technique uses a jacketed pan equipped with a baffle system. Tablets are placed into the sealed pan, an inert gas (i.e., nitrogen) is used to displace the air and then a vacuum is drawn.
947					
948 949			iv	· •	Dip Coating
949 950					Coating is applied to the substrate by dipping it into the
951					coating material. Drying is accomplished using pan coating
952					equipment.
953					
954			v.		Electrostatic Coating
955					
956					A strong electrostatic charge is applied to the surface of the
957					substrate. The coating material containing oppositely charged ionic
958					species is sprayed onto the substrate.
959					
960			vi	l <b>.</b>	Compression Coating
961 962					Refer to the Unit Dosing section of this document.
902					Refer to the Ohn Dosing section of this document.
963			vi	ii.	Ink-Based Printing
964					The application of contrasting colored polymer (ink) onto
965					the surface of a tablet or capsule.
966					
967			vi	iii.	Laser Etching
968					
969					The application of identifying markings onto the surface of a
970					tablet or capsule using laser-based technology.
971			:		
972 973			ix	•	Drilling
973 974					A drilling system typically is a custom built unit consisting of a
975					material handling system to orient and hold the solid dosage form,
976					a laser (or lasers), and optics (lenses, mirrors, deflectors, etc.) to
977					ablate the hole or holes, and controls. The drilling unit may include
978					debris extraction and inspection systems as well. The sorting,
979					orienting, and holding equipment commonly is provided by dosage
980					form printing equipment manufacturers, and is considered ancillary
981					in this use.
982			~ 1		
983	2.	Equip	ment Class	sificat	tion
984		-	Dor Cart		
985		a.	Pan Coati	mg	
986 987			Dan conti	ngen	bclasses primarily are distinguished by the pan configuration, the
987 988				0	ns, and/or the perforated device used to introduce process air for
700			Pan peno	n atio	ns, and/or the perforated device used to introduce process an for

989	drying purposes. Perforated coating systems include both batch and c	ontinuous
990	coating processes.	
991		
992	<ul> <li>Non-perforated (conventional) Coating System</li> </ul>	
993	Perforated Coating System	
994		
995	b. Gas Suspension	
996		
997	Gas suspension subclasses primarily are distinguished by the method	
998	by which the coating is applied to the substrate.	
999	by which the country is upplied to the substrate.	
1000	• Fluidized Bed with bottom spray mechanism	
1000	<ul> <li>Fluidized Bed with tangential spray mechanism</li> </ul>	
1001		
1003	Fluidized Bed with Wurster column	
1004	Spray Congealing/Drying	
1005		
1006	c. Vacuum Film Coating	
1007		
1008	Although there may be differences in the jacketed pan, baffle system, of	
1009	vacuum source, no vacuum film coating subclasses have been identifie	d.
1010		
1011	d. Dip Coating	
1012	~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~	
1013	Because of the custom design associated with this class of coating, no	dip
1014	coating subclasses or examples have been identified.	
1015		
1016	e. Electrostatic Coating	
1017		
1018	Because of the custom design associated with this class of coating, no	
1019	electrostatic coating subclasses or examples have been identified.	
1020		
1021	f. Compression Coating	
1022		
1023	Refer to the Unit Dosing section of this document.	
1024		
1025	g. Ink-Based Printing	
1026		
1027	Ink-based printing subclasses primarily are distinguished by the method	l by which
1028	the marking is applied to a capsule or tablet surface.	
1029		
1030	• Offset	
1031	• Ink Jet	
1032		
1033	h. Laser Etching (Printing)	
1034		

1035 1036 1037			-	er etching systems may differ from one another, no laser asses have been identified.
1038 1039		i.	Drilling	
1040 1041 1042			consequence	of producing the laser pulse that ablates the hole(s) is of no to the physical-chemical properties of the product. Therefore, no hrilling equipment subclasses have been identified.
1043	<b>X</b> 7		C SS INFOD	MATION
1044 1045	V.	SUPA	C-SS INFOR	MATION
1045		A.	Particle Size	Reduction/Separation
1047		1 10		Reduction Separation
1048	The s	same dei	finition and cla	ssification applies as described in section IV. A. for IR/MR
1049	produ			
1050				
1051		В.	Mixing	
1052				
1053	1.	Defini	tions	
1054				
1055		a.	Unit Operatio	n
1056			Mining. The	mention of nonticles relative to one enother to exhibit
1057 1058			0	reorientation of particles relative to one another to achieve randomness. This process can include wetting of solids by a liquid
1058			•	sion of discrete particles, or deagglomeration into a continuous
1059				and cooling via indirect conduction may be used in this operation
1060			-	ase mixing or stabilization.
1062			to inclinate pr	
1063		b.	Operating Prin	nciples
1064			1 0	1
1065			i.	Convection Mixing, Low Shear: Mixing process with a repeated
1066				pattern of cycling material from top to bottom, in which dispersion
1067				occurs under low power per unit mass through rotating low shear
1068				forces.
1069				
1070			ii.	Convection Mixing, High Shear: Mixing process with a repeated
1071				pattern of cycling material from top to bottom, in which dispersion
1072				occurs under high power per unit mass through rotating high shear
1073				forces.
1074				
1075			iii.	Roller Mixing (Milling): Mixing process by high mechanical
1076 1077				shearing action where compression stress is achieved by passing material between a series of rotating rolls. This is commonly
1077				material between a series of rotating rolls. This is commonly referred to as compression or roller milling.
1078				referred to as compression of roller mining.
10/9				

1080		iv. Static Mixing: Mixing process in which material passes through a
1081		tube with stationary baffles. The mixer is generally used in
1082		conjunction with an in-line pump.
1083 1084	2. Equip	ment Classification
1084	2. Equip	ment Classification
1085	a.	Convection Mixers, Low Shear
1087	u.	Convertion withous, Low Shour
1087		This group normally operates under low shear conditions and is broken down by
1089		impeller design and movement. Design can also include a jacketed vessel to
1090		facilitate heat transfer.
1091		
1092		Anchor or sweepgate
1093		• Impeller
1094		• Planetary
1095		
1096	b.	Convection Mixers, High Shear
1097		
1098		This group normally operates only under high shear conditions. Subclasses are
1099		differentiated by how the high shear is introduced into the material, such as by a
1100		dispersator with serrated blades or homogenizer with rotor stator.
1101		• Dispersator
1102 1103		<ul><li>Dispersator</li><li>Rotor stator</li></ul>
1103		• Kotor stator
1104	c.	Roller Mixers (Mills)
1105	с.	Koher Whitels (White)
1100		No roller mixer subclasses have been identified.
1108		
1109	d.	Static Mixers
1110		
1111		No static mixer subclasses have been identified.
$1112 \\ 1113$		
1114	Note: If a si	ngle piece of equipment is capable of performing multiple discrete unit operations,
1115		valuated solely for its ability to mix materials.
1116		
1117	С.	Emulsification
1118		
1119	1. Defini	tions
1120		Unit Operation
1121	a.	Unit Operation
1122 1123		Emulsification: The application of physical energy to a liquid system consisting of
1125		Emulsification: The application of physical energy to a liquid system consisting of at least two immiscible phases, causing one phase to be dispersed into the other.
1124		at least two miniscrole phases, eausing one phase to be dispersed into the other.
1125	h	Operating Principles
1120	0.	- r0 P0
-		

1128 1129 1130	r r			ear Emulsification: Use of low shear energy using cal mixing with an impeller to achieve a dispersion of the The effectiveness of this operation is especially dependent
1131			on prope	er formulation.
1132		::	II ah Ch	an Emploification. Use of high shear energy to
1133		ii.	-	ear Emulsification: Use of high shear energy to
1134				a dispersion of the immiscible phases. High shear can
1135			be achie	ved by the following means:
1136				N, M , M , M , M , M , M , M , M , M , M
1137				Stirring the mixture with a high speed chopper or
1138			S	aw-tooth dispersator.
1139				
1140				Passing the mixture through the gap between a high-
1141			S	speed rotor and a stationary stator.
1142			-	
1143				Passing the mixture through a small orifice at high pressure
1144				valve- type homogenizer) or through a small orifice at high
1145			-	pressure followed by impact against a hard surface or
1146				opposing stream (valve-impactor type homogenizer),
1147			С	causing sudden changes of pressure.
1148				
1149	2. Equip	ment Classifica	tion	
1150			1	
1151	a.	Low Shear Er	nulsifiers	
1152		41.1 1 1		
1153		-		ulsification equipment (mechanical stirrers or impellers)
1154			• •	fluid flow imparted to the mixture (axial-flow propeller or
1155		radial-flow tu	rbines), no	o subclasses have been defined.
1156			1	
1157	b.	High Shear E	nulsifiers	
1158		<b>a</b> 1 1 <b>a</b>		
1159			-	r emulsification equipment differ in the method used
1160		to generate hi	gh shear.	
1161				
1162		• Dispersate		
1163		• Rotor stat		
1164		• Valve or p	pressure h	omogenizer
1165				
1166				is capable of performing multiple discrete unit
1167	operations, t	he unit has beer	n evaluate	d solely for its ability to emulsify materials.
1168	D	Descration		
1169	D.	Deaeration		
1170	1 Daf	tions		
1171 1172	1. Defini	uions		
1173	a.	Unit Operatio	n	
1174		1		

1175 1176		Deaeration: The elimination of trapped gases to provide more accurate volumetric measurements and remove potentially reactive gases.					
1177 1178	b.	Operating Principles					
1179 1180		The use of vacuum or negative pressure, alone or in combination with mechanical					
1181		intervention or assistance.					
1182 1183	2. Equip	. Equipment Classification					
1184	2. Equip	neni Classification					
1185 1186	a.	Deaerators					
1180		Deaerator subclasses differ primarily in their air removal paths, either through the					
1188		bulk material or through a thin film, and in whether they use a batch or in-line					
1189 1190		process.					
1191		Off-Line or in-line					
1192		Vacuum vessel					
1193 1194	Note: If a si	ingle piece of equipment is capable of performing multiple discrete unit operations,					
1195		evaluated solely for its ability to deaerate materials.					
1196 1197	Е.	Transfer					
1197	<b>E</b> .	Transier					
1199	1. Defini	1. Definition					
1200 1201	a.	Unit Operation					
1201	u.						
1203 1204 1205		Transfer: The controlled movement or transfer of materials from one location to another.					
1206	b.	Operating Principles					
1207 1208		i. Passive: The movement of materials across a non-mechanically-					
1208		induced pressure gradient, usually through conduit or pipe.					
1210							
1211		ii. Active: The movement of materials across a mechanically-					
1212 1213		induced pressure gradient, usually through conduit or pipe.					
1214 1215	2. Equip	ment Classification					
1216 1217	a.	Low Shear					
1218		Active or passive material transfer, with a low degree of induced shear					
1219							
1220 1221	<ul><li>Diaphragm</li><li>Gravity</li></ul>						
1221	<ul> <li>Oravity</li> <li>Peristaltic</li> </ul>						
1223	• Piston						
1224	Pneumatic     Datating labo						
1225 1226		<ul><li>Rotating lobe</li><li>Screw or helical screw</li></ul>					
1220							
1228 1229	b.	High Shear					

	Active or mechanical material transfer with a high degree of induced shear					
	<ul> <li>Centrifugal or turbine</li> <li>Piston</li> <li>Rotating gear</li> </ul>					
pi lo ca	rodu ow o apab	ict or pa or high s ole of pe	artially manu shear class, d	ended to deal with the transfer of shear sensitive materials, including factured product. A single piece of equipment can be placed in either a epending on its operating parameters. If a single piece of equipment is altiple discrete unit operations, the unit has been evaluated solely for its ls.		
		F.	Packaging			
	1.	Defini	tions			
		a.	Unit Operat	tion		
		u.	ennt opera			
			i.	Holding: The process of storing product after completion of		
				manufacturing process and prior to filling final primary packs.		
			ii.	Transfer: The process of relocating bulk finished product from		
				holding to filling equipment using pipe, hose, pumps and/or other		
				associated components.		
			iii.	Filling: The delivery of target weight or volume of bulk finished		
			111.	product to primary pack containers		
				product to primary pack containers		
			iv.	Sealing: A device or process for closing and/or sealing primary		
				pack containers following the filling process.		
		h	Operating I	Dringinlag		
		υ.	Operating F	metpies		
			i.	Holding: The storage of liquid, semi-solids, or product		
			1.	materials in a vessel that may or may not have temperature		
				control and/or agitation.		
			ii.	Transfer: The controlled movement or transfer of materials		
				from one location to another.		
			iii.	Filling: Filling operating principles involve several associated		
				subprinciples. The primary package can be precleaned to remove		
				particulates or other materials by the use of ionized air, vacuum,		
				or inversion. A holding vessel equipped with an auger, gravity, or		
				pressure material feeding system should be used. The vessel may		
				or may not be able to control temperature and/or agitation. Actual		
				filling of the dosage form into primary containers can involve a		
				metering system based on an auger, gear, orifice, peristaltic, or		
				piston pump. A head-space blanketing system can also be used.		

1279		
1280		g: Primary packages can be sealed using a variety of
1281		ods, including conducted heat and electromagnetic
1282	(indu	ction or microwave) or mechanical manipulation (crimping
1283	or tor	quing).
1284		
1285	2. Equipment Classification	
1286	TT 11	
1287	a. Holders	
1288		
1289	• •	ssels can differ in their geometry and ability to control
1290		ion, their primary differences are based on how materials
1291	are fed.	
1292		
1293	• Auger	
1294	• Gravity	•
1295	Pneumatic (nitro)	gen, air, etc.)
1296		
1297	b. Fillers	
1298		·
1299	1 · ·	ces in filling equipment are based on how materials
1300	are metered.	
1301		
1302	• Auger	
1303	• Gear pump	
1304	• Orifice	
1305	Peristaltic pump	
1306	• Piston	
1307		
1308	c. Sealers	
1309		
1310	-	imary container sealing are based on how energy is
1311	transferred or applied	l.
1312		
1313	• Heat	
1314	Induction	
1315	<ul> <li>Microwave</li> </ul>	
1316	Mechanical or cr	mping
1317	• Torque	
1318		
1319		