Guidance for Industry

SUPAC-IR: Immediate Release Solid Oral Dosage Forms

Manufacturing Equipment Addendum

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
October 1997
CMC 9

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TABLE OF CONTENTS

GUIDANCE FOR INDUSTRY [1]

Supac-IR: Immediate Release Solid Oral Dosage Forms Manufacturing Equipment Addendum

I. INTRODUCTION

The purpose of this guidance is to provide recommendations to pharmaceutical manufacturers using the Center for Drug Evaluation and Research's *Guidance for Industry: Immediate Release Solid Oral Dosage Forms — Scale-Up and Post-Approval Changes: Chemistry, Manufacturing and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation* (SUPAC-IR), which published in November 1995. This document was developed by the U.S. Food and Drug Administration (FDA) with the assistance of the International Society of Pharmaceutical Engineering (ISPE).

The document should be used in conjunction with the SUPAC-IR guidance document in determining what documentation should be submitted to FDA regarding equipment changes made in accordance with the recommendations in sections V and VI.A of the SUPAC-IR guidance document. The SUPAC-IR guidance document defines (1) levels of change; (2) recommended chemistry, manufacturing, and controls tests for each level of change; (3) in vitro dissolution tests and/or in vivo bioequivalence tests for each level of change; and (4) documentation that should support the change for new drug applications (NDAs), abbreviated new drug applications (ANDAs), and abbreviated antibiotic applications (AADAs).
This document is only an aid and, in some cases, specific equipment may not be listed. It does, however, include a representative list of equipment commonly used in the industry. The guidance does not address equipment that has been modified by a pharmaceutical manufacturer to fit its specific needs. If questions arise in using this guidance document please contact the appropriate reviewing office at CDER.

Although this guidance does not discuss validation, any changes should be validated in accordance with current good manufacturing practices (cGMPs) and the resulting data will be reviewed by field investigators during routine GMP inspections. The information is presented in broad categories of unit operation (blending and mixing, drying, particle size reduction/separation, granulation, unit dosage, coating and printing, soft gelatin capsule encapsulation). Definitions and classification are provided. For each operation, a table is presented that categorizes equipment by

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[1]This guidance has been prepared under the auspices of the Chemistry, Manufacturing, and Controls Coordinating Committee in the Center for Drug Evaluation and Research (CDER) and the Office of Regulatory Affairs (ORA) at the Food and Drug Administration with the assistance of the International Society of Pharmaceutical Engineering (ISPE). This guidance represents the Agency's current thinking on equipment changes under SUPAC-IR. It does not create or confer any rights for or on any person and does not operate to bind the FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations or both.

class (operating principle) and subclass (design characteristic). Examples are given within the subclasses.

Equipment within the same class and subclass would be considered to have the same design and operating principle under SUPAC-IR. Therefore, for example, a change from one type of diffusion mixer (e.g, V-blender from manufacturer A) to another diffusion mixer (e.g., V-blender from manufacturer B) generally would not represent a change in operating principle and would, therefore, be considered to be the same under SUPAC-IR.

Change from equipment in one class to equipment in a different class would usually be considered a change in design and operating principle. For example, a change from a V-blender to a ribbon blender demonstrates a change in the operating principle from diffusion blending to convection blending and would be considered to be different under SUPAC-IR.

Applicants should carefully consider and evaluate on a case-by-case basis changes in equipment that are in the same class, but different subclass. In many situations, this type of change in equipment would be considered similar. For example, within the Blending and Mixing section, under the Diffusion Mixers Class, a change from a V-blender (sub-class) to a Bin tumbler (sub-class) represents a change within a class and between sub-classes. Provided the manufacturing process with the new equipment is validated, this change would likely not need a pre-approval supplement. The applicant should have available at the time of the change the scientific data and rationale used to make this determination. This information is subject to FDA review at its discretion. It is up to the applicant to determine the filing requirement.

This guidance will be updated as needed to reflect the introduction and discontinuation of specific types of manufacturing equipment. Manufacturers of equipment are encouraged to help keep the document current by communicating changes to the Agency and by making suggestions regarding what equipment should be considered to be within the same class or subclass. The submitted information will be reviewed by FDA and incorporated in an updated guidance document as appropriate.

II. PARTICLE SIZE REDUCTION/SEPARATION

A. Definitions

1. Unit Operations

a. Particle Size Reduction: The mechanical process of breaking particles into smaller pieces via one or more particle size reduction mechanisms. The mechanical process used generally is referred to as milling.

i. Particle - Refers to either a discrete crystal or a grouping of crystals, generally known as an agglomerate.

ii. Particle Size Reduction Mechanisms

- Impact - Particle size reduction by applying an instantaneous force perpendicular to the particle/agglomerate surface. The force can result from particle-to-particle or particle-to-mill surface collision.

- Attrition - Particle size reduction by applying a force in a direction parallel to the particle surface.

- Compression - Particle size reduction by applying a force slowly (as compared to Impact) to the particle surface in a direction toward the center of the particle.

- Cutting - Particle size reduction by applying a shearing force to a material.

b. Particle Separation: Particle size classification according to particle size alone.

2. Operating Principles

a. Fluid Energy Milling

Particles are reduced in size as a result of high-speed particle-to-particle impact and/or attrition; also known as micronizing.

b. Impact Milling

Particles are reduced in size by high-speed mechanical impact or impact with other particles; also known as milling, pulverizing, or comminuting.

c. Cutting

Particles are reduced in size by mechanical shearing.

d. Compression Milling

Particles are reduced in sized by compression stress and shear between two surfaces.

e. Screening

Particles are reduced in size by mechanically induced attrition through a screen. This process commonly is referred to as milling or deagglomeration.

f. Tumble Milling

Particles are reduced in size by attrition utilizing grinding media.

g. Separating

Particles are segregated based upon particle size alone and without any significant particle size reduction. This process commonly is referred to as screening or bolting.

B. Equipment Classifications

1. Fluid Energy Mills

Fluid energy mill subclasses have no moving parts and primarily are distinguished from one another by the configuration and/or shape of their chambers, nozzles, and classifiers.

- Tangential Jet
- Loop/Oval
- Opposed Jet
- Opposed Jet with Dynamic Classifier
- Fluidized Bed
- Fixed Target
- Moving Target

2. Impact Mills

Impact mill subclasses primarily are distinguished from one another by the configuration of the grinding heads, chamber grinding liners (if any), and classifiers.

- Hammer Air Swept
- Hammer Conventional
- Pin/Disc
- Cage

3. Cutting Mills

   Although cutting mills may differ from one another in whether the knives are stationary or fixed and the classifier configuration, no cutting mill subclasses have been identified.

4. Compression Mills

   Although compression mills may differ from one another in whether one or both surfaces are moving, no compression mill subclasses have been identified.

5. Screening Mills

   Screening mill subclasses primarily are distinguished from one another by the rotating element.

   - Rotating Impeller
   - Rotating Screen
   - Oscillating

6. Tumbling Mills

   Tumbling mill subclasses primarily are distinguished from one another by the grinding media used and by whether the mill is vibrated.

   - Ball Media
   - Rod Media
   - Vibrating

7. Separators

   Separator subclasses primarily are distinguished from one another by the mechanical means used to induce particle movement.

   - Vibratory/Shaker
   - Centrifugal

Table 1 Unit Operation - Particle Size Reduction

Class	Subclass	Examples
Fluid Energy Mills	Tangential Jet	Alpine (Hosokawa) Fluid Energy Aljet Sturtevant
	Loop/Oval	Fluid Energy Aljet
	Opposed Jet	Garlock
	Opposed Jet with Dynamic Classifier	Alpine (Hosokawa) Fluid Energy Aljet
	Fluidized Bed	None Identified
	Fixed Target	None Identified
	Moving Target	None Identified
Impact Mills	Hammer Air Swept	Alpine (Hosokawa) Bepex (Hosokawa) Sturtevant
	Hammer Conventional	Alpine (Hosokawa) Fitzpatrick Fluid Air Mikro (Hosokawa) Rietz (Hosokawa) Stokes-Merrill
	Pin/Disc	Alpine (Hosokawa) Kemutec Sturtevant
	Cage	Stedman
Cutting Mills	None Identified	Alpine (Hosokawa) Fitzpatrick Urschel
Compression Mills	None Identified	MCA International

Table 1 Unit Operation - Particle Size Reduction (cont.)

Class	Subclass	Examples
Screening Mills	Rotating Impeller	Bepex (Hosokawa) Fitzpatrick Fluid Air Kemutec Quadro Stokes-Merrill Zanchetta (Romaco)
	Rotating Screen	Glatt
	Oscillating	Bepex (Hosokawa) Frewitt Jackson-Crockatt Stokes-Merrill Vector
Tumbling Mills	Ball Media	US Stoneware
	Rod Media	None Identified
	Vibrating	Sweco

Table 2 Unit Operation - Separation

Class	Subclass	Examples
Separators	Vibratory/Shaker	Allgaier McLanahan Rotex Russell Finex Sweco VortiSiv
	Centrifugal	AZO Kason Kemutec Sweco

III. BLENDING AND MIXING

A. Definitions

1. Unit Operations

Blending and Mixing: The reorientation of particles relative to one another in order to achieve uniformity.

2. Operating Principles

a. Diffusion Blending (Tumble)

Particles are reoriented in relation to one another when they are placed in random motion and interparticular friction is reduced as the result of bed expansion (usually within a rotating container); also known as tumble blending.

b. Convection Mixing

Particles are reoriented in relation to one another as a result of mechanical movement; also known as paddle or plow mixing.

c. Pneumatic Mixing

Particles are reoriented in relation to one another as a result of the expansion of a powder bed by gas.

B. Equipment Classifications

1. Diffusion Mixers (Tumble)

Diffusion mixer subclasses primarily are distinguished by geometric shape and the positioning of the axis of rotation.

- V-blenders
- Double Cone Blenders
- Slant Cone Blenders
- Cube Blenders
- Bin Blenders

- Horizontal/Vertical/Drum Blenders
- Static Continuous Blenders
- Dynamic Continuous Blenders

2. Convection Mixers

   Convection blender subclasses primarily are distinguished by vessel shape and impeller geometry:

   - Ribbon Blenders
   - Orbiting Screw Blenders
   - Planetary Blenders
   - Forberg Blenders
   - Horizontal Double Arm Blenders
   - Horizontal High Intensity Mixers
   - Vertical High Intensity Mixers
   - Diffusion Mixers (Tumble) with Intensifier/Agitator

3. Pneumatic Mixers

   Although pneumatic mixers may differ from one another in vessel geometry, air nozzle type, and air nozzle configuration, no pneumatic mixer subclasses have been identified.

Table 1 Unit Operation - Blending and Mixing

Class	Subclass	Examples
Diffusion Mixers (Tumble)	V-Blenders	Aaron Paul O. Abbe Gemco Jaygo Kemutec Lleal Lowe O'Hara Patterson-Kelley Pneuvac Zanchetta (Romaco)
	Double Cone Blenders	Aaron Paul O. Abbe Gemco Jaygo Kemutec Lleal Lowe MO Industries Patterson- Kelley Pneuvac ServoLift Zanchetta (Romaco)
	Slant Cone Blenders	Gemco Lleal Patterson-Kelley
	Cube Blenders	Lightnin ServoLift Zanchetta (Romaco)

Table 1 Unit Operation - Blending & Mixing (cont.)

Class	Subclass	Examples
Diffusion Mixers (Tumble) (cont.)	Bin Blenders	Paul O. Abbe L. B. Bohle Cora International Creative Design & Machine Custom Metal Craft GEI-Gallay (GEI North America/Patriot) Gemco Glatt Jenike & Johanson Kemutec Matcon, USA Scholl (MO Industries) ServoLift Tote Systems Zanchetta (Romaco)
	Horizontal/Vertical/Drum Blenders	Munson Mill Machinery
	Static Continuous Blenders	Ross
	Dynamic Continuous Blenders	Patterson-Kelley
Convection Mixers	Ribbon Blenders	Aaron Paul O. Abbe Automatic Industry Machines Azo-Ruberg Custom Metal Craft Jaygo Kemutec Lowe Pneuvac Ross Vrieco-Nauta (Hosokawa)
	Orbiting Screw Blenders	Aaron Jaygo Littleford Day Ross Vrieco-Nauta (Hosokawa)

Table 1 Unit Operation - Blending & Mixing (cont.)

Class	Subclass	Examples
Convection Mixers (cont.)	Planetary Blenders	Aaron Aeschbach AMF GEI-Collette (GEI North America/Vector) Hobart Jaygo Littleford Day Ross Vrieco
	Forberg Blenders	Paul O. Abbe Dynamic Air
	Horizontal Double Arm Blenders	Aaron Paul O. Abbe Custom Metal Craft Dynamic Air Jaygo Kemutec Littleford Day Ross Sigma Teledyne Readco
	Horizontal High Intensity Mixers	Littleford Day
	Vertical High Intensity Mixers	Aeromatic-Fielder (GEA-Niro) APV L.B. Bohle Dierks & Shone GEI-Collette (GEI North America/Vector) Key International Littleford Day Powrex (Glatt) Zanchetta (Romaco)
	Diffusion Mixers (Tumble) with Intensifier/Agitator	Paul O. Abbe Gemco Patterson-Kelley
Pneumatic Mixers	None Identified	Dynamic Air Reimelt

IV. GRANULATION

A. Definitions

1. Unit Operations

Granulation: The process of creating granules. The powder morphology is modified through the use of either a liquid that causes particles to bind through capillary forces or dry compaction forces. The process will result in one or more of the following powder properties: enhanced flow; increased compressibility; densification; alteration of physical appearance to more spherical, uniform, or larger particles; and/or enhanced hydrophilic surface properties.

2. Operating Principles

a. Dry Granulation

Dry powder densification and/or agglomeration by direct physical compaction.

b. Wet High-Shear Granulation

Powder densification and/or agglomeration by the incorporation of a granulation fluid into the powder with high-power-per-unit mass, through rotating high-shear forces.

c. Wet Low-Shear Granulation

Powder densification and/or agglomeration by the incorporation of a granulation fluid into the powder with low-power-per-unit mass, through rotating low-shear forces.

d. Low-Shear Tumble Granulation

Powder densification and/or agglomeration by the incorporation of a granulation fluid into the powder with low-power-per-unit mass, through rotation of the container vessel and/or intensifier bar.

e. Extrusion Granulation

Plasticization of solids or wetted mass of solids and granulation fluid with linear shear through a sized orifice using a pressure gradient.

f. Rotary Granulation

Powder densification, agglomeration, and/or spheronization, incorporating and subsequently drying a granulation fluid while the powder is fluidized in a cylindrical pattern by a rotating disk, with air flowing between the disk and vessel walls.

g. Fluid Bed Granulation

Powder densification and/or agglomeration with little or no shear by direct granulation fluid atomization and impingement on solids, while suspended by a controlled gas stream, with simultaneous drying.

h. Spray Dry Granulation

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.

B. Equipment Classification

1. Dry Granulator

Dry granulator subclasses primarily are distinguished by the densification force application mechanism.

- Slugging
- Roller Compaction

2. Wet High-Shear Granulator

Wet high-shear granulator subclasses primarily are distinguished by the geometric positioning of the primary impellers; impellers can be top, bottom, or side driven.

- Top or Bottom Driven
- Side Driven

3. Wet Low-Shear Granulator

   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.

   - Planetary
   - Kneading
   - Screw

4. Low-Shear Tumble Granulator

   Although low-shear tumble granulators may differ from one another in vessel geometry and type of dispersion or intensifier bar, no low-shear tumble granulator subclasses have been identified.

5. Extrusion Granulator

   Extrusion granulator subclasses primarily are distinguished by the orientation of extrusion surfaces and driving pressure production mechanism.

   - Radial or Basket
   - Axial
   - Ram
   - Roller, Gear, or Pelletizer

6. Rotary Granulator

   Rotary granulator subclasses primarily are distinguished by their structural architecture. They have either an open top architecture, like a rotary granulator, or a closed top architecture, like a fluid bed dryer.

   - Open
   - Closed

7. Fluid Bed Granulator

   Although fluid bed granulators may differ from one another in geometry, operating pressures, and other conditions, no fluid bed granulator subclasses have been identified.

8. Spray Dry Granulator

   Although spray dry granulators may differ from one another in geometry, operating pressures, and other conditions, no spray dry granulator subclasses have been identified.

Note:
If a single piece of equipment is capable of performing multiple discrete unit operations (mixing, granulating, drying), the unit was evaluated solely for its ability to granulate. If multifunctional units were incapable of discrete steps (fluid bed granulator/drier), the unit was evaluated as an integrated unit.

Table 1 Unit Operation - Granulation

Class	Subclass	Examples
Dry Granulator	Slugging	*Various*
	Roller Compaction	Alexanderwerk Bepex (Hosokawa) Fitzpatrick
Wet High Shear Granulator	Top Driven, or Bottom Driven	Aeromatic-Fielder (GEA-Niro) Baker-Perkins L.B. Bohle Diosna GEI-Collette (GEI North America/Vector) Key Littleford Day Powrex (Glatt) Werner & Pfeiderer Zanchetta (Romaco)
	Side Driven	Lodige
Wet Low Shear Granulator	Planetary	Aaron Aeschbach AMF GEI-Collette (GEI North America/Vector) Hobart Jaygo Littleford Day Ross Vrieco
	Kneading	Aaron Paul O. Abbe Custom Metal Craft Dynamic Air Jaygo Kemutec Littleford Day Ross Sigma Teledyne Readco
	Screw	Vrieco-Nauta (Hosokawa)
Low Shear Tumble Granulator	Slant Cone, or Double Cone, or V-Blender	Paul O. Abbe Gemco Patterson-Kelley

Table 1 Unit Operation - Granulation (cont.)

Class	Subclass	Examples
Extrusion Granulator	Radial or Basket	Alexanderwerk GEA Niro LCI Ross
	Axial	Bepex (Hosokawa) Gabler LCI
	Ram	LCI
	Roller, Gear, or Pelletizer	Alexanderwerk Bepex (Hosokawa)
Rotary Granulator	Open	Freund (Vector)
	Closed	Aeromatic-Fielder (GEA Niro) Glatt LCI Vector
Fluid Bed Granulator	None Identified	Aeromatic-Fielder (GEA Niro) Allgaier APV BWI Hüttlin (Thomas Engineering) Fitzpatrick Fluid Air Glatt Heinen Vector
Spray Dry Granulator	None Identified	Allgaier GEA Niro Glatt Heinen

V. DRYING

A. Definitions

1. Unit Operation

   Drying: The removal of a liquid from a solid by evaporation.

2. Operating Principles

   a. Direct Heating, Static Solids Bed

      Heat transfer is accomplished by direct contact between the wet solids and hot gases. The vaporized liquid is carried away by the drying gases. There is no relative motion among solid particles. The solids bed exists as a dense bed, with the particles resting upon one another.

   b. Direct Heating, Moving Solids Bed

      Heat transfer is accomplished by direct contact between the wet solids and hot gases. The vaporized liquid is carried away by the drying gases. Solids motion is achieved by either mechanical agitation or gravity force, which slightly expands the bed enough to flow one particle over another.

   c. Direct Heating, Fluidized Solids Bed

      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.

   d. Direct Heating, Dilute Solids Bed, Spray Drying

      Heat transfer is accomplished by direct contact between a highly dispersed liquid and hot gases. The feed liquid may be a solution, 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 one another.

e. Direct Heating, Dilute Solids Bed, Flash Drying

Heat transfer is accomplished by direct contact between wet solids and hot gases. The solid mass is suspended in a finely divided state in a high-velocity and high-temperature gas stream. The vaporized liquid is carried away by the drying gases.

f. Indirect Conduction, Moving Solids Bed

Heat transfer to the wet solid is through a retaining wall. The vaporized liquid is removed independently from the heating medium. Solids motion is achieved by either mechanical agitation or gravity force, which slightly expands the bed enough to flow one particle over another.

g. Indirect Conduction, Static Solids Bed

Heat transfer to the wet solid is through a retaining wall. The vaporized liquid is removed independently from the heating medium. There is no relative motion among solid particles. The solids bed exists as a dense bed, with the particles resting upon one another.

h. Indirect Conduction, Lyophilization

Drying in which the water vapor sublimes from the product after freezing.

i. Gas Stripping

Heat transfer is a combination of direct and indirect heating. The solids motion is achieved by agitation and the bed is partially fluidized.

j. Indirect Radiant, Moving Solids Bed

Heat transfer is accomplished with varying wavelengths of energy. Vaporized liquid is removed independently from the solids bed. The solids motion is achieved by mechanical agitation, which slightly expands the bed enough to flow one particle over one another. This process commonly is referred to as microwave drying.

B. Equipment Classifications

1. Direct Heating, Static Solids Bed

Static solids bed subclasses primarily are distinguished by the method of moving the solids into the dryer.

- Tray and Truck
- Belt

2. Direct Heating, Moving Solids Bed

Moving solids bed subclasses primarily are distinguished by the method or technology for moving the solids bed.

- Rotating Tray
- Horizontal Vibrating Conveyor

3. Direct Heating, Fluidized Solids Bed (Fluid Bed Dryer)

Although fluid bed dryers may differ from one another in geometry, operating pressures, and other conditions, no fluidized solids bed dryer subclasses have been identified.

4. Direct Heating, Dilute Solids Bed, Spray Dryer

Although spray dryers may differ from one another in geometry, operating pressures, and other conditions, no spray dryer subclasses have been identified.

5. Direct Heating, Dilute Solids Bed, Flash Dryer

Although flash dryers may differ from one another in geometry, operating pressures, and other conditions, no flash dryer subclasses have been identified.

6. Indirect Conduction Heating, Moving Solids Bed

   Moving solids bed subclasses primarily are distinguished by the method or technology for moving the solids bed.

   - Paddle
   - Rotary (Tumble)
   - Agitation

7. Indirect Conduction Heating, Static Solids Beds

   No indirect heating, static solids bed shelf dryer subclasses have been identified.

8. Indirect Conduction, Lyophilization

   No lyophilizer subclasses have been identified.

9. Gas Stripping

   Although gas stripping dryers may differ from one another in geometry, shape of agitator, and how fluidizing gas is moved through the bed, no gas stripping dryer subclasses have been identified.

10. Indirect Radiant Heating, Moving Solids Bed (Microwave Dryer)

   Although microwave dryers may differ from one another in vessel geometry and the way microwaves are directed into the solids, no indirect radiant heating, moving solids bed dryer subclasses have been identified.

Note:
If a single piece of equipment is capable of performing multiple discrete unit operations (mixing, granulating, drying), the unit was evaluated solely for its ability to dry. The drying equipment was sorted into similar classes of equipment, based upon the method of heat transfer and the dynamics of the solids bed.

Table 1 Unit Operation - Drying

<table>
<tr><th>Class</th><th>Subclass</th><th>Examples</th></tr>
<tr><td rowspan="2">Direct Heating, Static Solids Bed</td><td>Tray and Truck</td><td>Colton
Despatch
Gruenberg
Hot Pack
Lydon
O’Hara
Proctor & Schwartz
Trent</td></tr>
<tr><td>Belt</td><td>Despatch
Proctor & Schwartz</td></tr>
<tr><td rowspan="2">Direct Heating, Moving Solids Bed</td><td>Rotating Tray</td><td>Krauss Maffei
Wyssmont</td></tr>
<tr><td>Horizontal Vibrating Conveyor</td><td>Carrier
Witte</td></tr>
<tr><td>Direct Heating, Fluidized Solids Bed (Fluid Bed Dryer)</td><td>None Identified</td><td>Aeromatic-Fielder (GEA-Niro)
Allgaier
APV
BWI Hüttlin (Thomas Engineering)
Fitzpatrick
Fluid Air
Glatt
Heinen
Vector</td></tr>
<tr><td>Direct Heating, Dilute Solids Bed, Spray Dryer</td><td>None Identified</td><td>Allgaier
APV
BWI Hüttlin (Thomas Engineering)
GEA-Niro
Glatt</td></tr>
<tr><td>Direct Heating, Dilute Solids Bed, Flash Dryer</td><td>None Identified</td><td>Allgaier
APV
GEA-Niro
Micron (Hosokawa)</td></tr>
</table>

Table 1 Unit Operation - Drying (cont.)

Class	Subclass	Examples
Indirect Conduction, Moving Solids Bed	Paddle	Bepex (Hosokawa) Jaygo
	Rotary (Tumble)	Paul O. Abbe Gemco Glatt Littleford Day Patterson-Kelley Zanchetta (Romaco)
	Agitation	L. B. Bohle Diosna GEI-Collette (GEI North America) Krauss Maffei Vrieco-Nauta (Hosokawa) Zanchetta (Romaco)
Indirect Conduction, Static Solids Bed	None Identified	Hull
Indirect Conduction, Lyophilization	None Identified	Amsco Hull Serail Stokes
Gas Stripping	None Identified	Aeromatic-Fielder (GEA-Niro) L.B. Bohle Diosna GEI-Collette (GEI North America) Zanchetta (Romaco)
Indirect Radiant Heating, Moving Solids Bed (Microwave Dryer)	None Identified	Aeromatic-Fielder (GEA-Niro) L. B. Bohle Diosna GEI-Collette (GEI North America)

VI. UNIT DOSING

A. Definitions

1. Unit Operation

   Unit Dosing: The division of a powder blend into uniform single portions for delivery to patients.

2. Operating Principles

   a. Tabletting

      The division of a powder blend in which compression force is applied to form a single unit dose.

   b. Encapsulating

      The division of a powder blend into a hard gelatin capsule. Encapsulators should all have the following operating principles in common: rectification (orientation of the hard gelatin capsules), separation of capsule caps from bodies, dosing of fill material/formulation, rejoining of caps and bodies, and ejection of filled capsules.

   c. Powder Filling

      Division of a powder blend into a container closure system.

B. Equipment Classifications

1. Tablet Press

   Tablet press subclasses primarily are distinguished from one another by the method that the powder blend is delivered to the die cavity. Tablet presses can deliver powders without mechanical assistance (gravity), with mechanical assistance (power assisted), by rotational forces (centrifugal), and in two different locations where a tablet core is formed and subsequently an outer layer of coating material is applied (compression coating).

   - Gravity
   - Power Assisted

- Centrifugal
- Compression Coating

2. Encapsulator

Encapsulator subclasses primarily are distinguished from one another by the method that is used for forming the powder blend into the slug. Encapsulators can deliver powders with a rotating auger, vacuum, vibration of perforated plate, tamping into a bored disk (dosing disk), or cylindrical tubes fitted with pistons (dosator).

- Auger
- Vacuum
- Vibratory
- Dosing Disk
- Dosator

3. Powder Filler

Subclasses of powder fillers primarily are distinguished by the method used to achieve the predetermined amount for container fill. Powders can be delivered by vacuum and compressed air (vacuum) or by auger.

- Vacuum
- Auger

Table 1 Unit Dosing

Class	Subclass	Examples
Tablet Press	Gravity	Colton (Vector) Manesty (Thomas Engineering) Stokes
	Power Assisted	Colton (Vector) Courtoy (AC Compacting) Fette Hata (Elizabeth Carbide) Kikisui Kilian Manesty (Thomas Engineering)
	Centrifugal	Comprima (IMA)
	Compression Coating	Manesty (Thomas Engineering) Kilian
Encapsulator	Auger	Capsugel Type B Elanco No. 8
	Vacuum	Perry
	Vibratory	Osaka (Sharpley-Stokes)
	Dosing Disk	H&K/ Bosch Index
	Dosator	Macofar (Romaco) MG2 Zanasi/Pharmatic/IMA
Powder Filler	Vacuum	Bosch Perry Zanasi
	Auger	All-Fill Calumatic

VII. GELATIN CAPSULES

A. Definitions

1. Unit Operations

a. Gel Mass Preparation: The manufacture of a homogeneous, degassed liquid mass (solution) of gelatin, plasticizer, water, and other additives, either in solution or suspension, such as colorants, pigments, flavors, preservatives, etc., that comprise a unique functional gel shell formation. The operation may be performed in discreet steps or by continuous processing. Minor components can be added after the liquid gel mass is made.

b. Fill Mixing: The mixing of either liquids or solids with other liquids to form a solution; blending of limited solubility solid(s) with a liquid carrier and suspending agents used to stabilize the blend to form a suspension; or the uniform combination of dry inert and drug active substances to form a dry powder fill suitable for encapsulation. The reader should refer to the other sections of this document for dry fill manufacture.

c. Core Enrobing: The gelatin coating of gravity or force fed pre-formed tablets or caplets.

d. Encapsulation: The continuous casting of gel ribbons, with liquid fill material being injected between the gel ribbons using a positive displacement pump or, for dry materials being gravity or force fed with capsule formation using a rotary die.

e. 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.

f. Drying: The removal of the majority of water from the capsule's gel shell by tumbling and subsequent tray drying using conditioned air, which enhances the size, shape, and shell physical properties of the final product. The drying 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.

g. Inspection/Sorting: The process wherein undesirable capsules are removed, including misshapen, leaking, and unfilled capsules as well as agglomerates of capsules.

h. Printing: The marking of a capsule surface for the purpose of product identification, using a suitable printing media or method.

2. Operating Principles

a. Mixing

The combination of solid and liquid components, including suspending aid(s) at either ambient or elevated temperatures to form a solution, suspension, or dry powder blend for the manufacture of gel mass or fill material. Mixing also includes the incorporation of minor components into the liquid gel mass.

b. Deaggregation

The removal of aggregates using a suitable homogenizer/mill to provide a pumpable fill material. The procedure has minimal effect on the particle size distribution of the initial solid component(s), and is viewed as a processing aid.[2]

c. Deaeration

The removal of entrapped air from either the gel mass or fill material, solution or suspension. This process can take place in either the mixing vessel, through the application of vacuum, or a separate off-line step.

d. Holding

The storage of liquid gel mass or fill material in a vessel, with a mixer or without, prior to encapsulation, which also may be equipped with a jacket for either heating or cooling.

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[2]Carstensen, J. T., "Theory of Pharmaceutical Systems, Volume 11 Heterogeneous Systems," *Academic Press*, New York, NY, 1973, p 51.

e. Encapsulation

The formation of capsules using a rotary die machine.[3]

f. Inspection/Sorting

The physical removal of misshapen, leaking, or agglomerated capsules, using either a manual or automatic operation.

g. Printing

The user of this document is asked to refer to the coating/printing section, in which the use of various pieces of equipment are defined and categorized.

B. Equipment Classifications

1. Mixers and Mixing Vessels

Mixer and mixing vessel subclasses primarily are distinguished by the mixing energy, mixer type, and whether a jacketed vessel with vacuum capabilities is used in conjunction with a specific mixer.

- Low Energy Mixer
- High Energy Mixer
- Planetary
- Jacketed Vessel With and Without Vacuum
- Conventional

2. Deaggregators

Deaggregator subclasses primarily are distinguished by the type of mechanical action imparted to the material.

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[3]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.

- Rotor/Stator
- Roller
- Cutting Mills
- Stone Mills
- Tumbling Mills

3. Deaerators

   Deaerator subclasses primarily are distinguished by the air removal path, either through the bulk or through a thin film, and whether it is a batch or in-line process.

   - Vacuum Vessel
   - Off Line/In Line

4. Holding Vessels

   Although holding vessels may differ from one another, based upon whether they are jacketed, with and without integrated mixing capabilities, no holding vessel subclasses have beeen identified.

5. Encapsulators

   Encapsulator subclasses primarily are distinguished by the method used to inject the fill material.

   - Positive Displacement Pump
   - Gravity or Force Fed

6. Inspection/Sorting

   Inspection/sorting equipment subclasses primarily are distinguished by the method used to present the capsule for viewing and mechanical method of separation.

   - Belt
   - Vibratory
   - Roller
   - Rotary Table
   - Electromechanical

Table 1 Unit Operation - Soft Gelatin Capsules

Class	Subclass	Examples
Mixers and Mixing Vessels	Low Energy	GEI-Collette (GEI North America/Vector) GEI-Kreiger (GEI North America) Hobart Koruma (Romaco) Lightnin Moorhouse-Cowles Quadro
	High Energy	Cowles GEI-Collette (GEI North America/Vector) Koruma (Romaco)
	Planetary	Aaron Aeschbach AMF GEI-Collette (GEI North America/Vector) Hobart Jaygo Littleford Day Ross Vrieco
	Jacketed with and without Vacuum	Becomix Fryma GEI-Kreiger (GEI North America) Hicks Lee Industries Paul Mueller Co. Ross Koruma (Romaco)
	Conventional	Lee Industries

Table 1 Unit Operation - Soft Gelatin Capsules (cont.)

Class	Subclass	Examples
Deaggregators	Rotor Stator	Barinco Greerco Koruma (Romaco)
	Roller	Stokes-Merrill
	Cutting Mills	Alpine(Hosokawa) Fitzpatrick Urschel
	Stone Mills	Fryma Koruma (Romaco)
	Tumbling Mills	Paul O. Abbe Fryma Premier Corp. U.S. Stoneware
Deaerators	Vacuum Vessel	Fryma GEI-Kreiger (GEI North America) Koruma (Romaco) Lee Industries Paul Mueller Co.
	Off Line/In Line	The Cornell Machine Co. Fryma Koruma (Romaco)
Holding Vessels	Jacketed Vessel with and without Mixing System	GEI-Kreiger (GEI North America) Koruma (Romaco) Lee Industries

Table 1 Unit Operation - Soft Gelatin Capsules (cont.)

Class	Subclass	Examples
Encapsulators	Positive Displacement Pump	Chang Sung Gaberino International Consultants Higuchi, Inc. USA Hypak Industries In House Construction J.B. Engineering Technopar Equipment & Svcs., Ltd
	Gravity or Force Feed	Accogel® (Stern Machine)
Inspection/Sorting	Belt	Lakso Merrill
	Vibratory	Stokes
	Roller	Maschimpex
	Rotary Table	Lakso Merrill
	ElectroMechanical	Mocon

VIII. COATING/PRINTING

A. Definitions

1. Unit Operation

a. Coating: The uniform deposition of a layer of material on or around a solid dosage form, or component thereof, to:

- protect the drug from its surrounding environment (air, moisture, and light), with a view to improving stability.
- mask unpleasant taste, odor, or color of the drug.
- increase the ease of ingesting the product for the patient.
- impart a characteristic appearance to the tablets, which facilitates product identification and aids patient compliance.
- provide physical protection to facilitate handling. This includes minimizing dust generation in subsequent unit operations.
- reduce the risk of interaction between incompatible components. This would be achieved by coating one or more of the offending ingredients.

The coating material deposition typically is accomplished through one of four major techniques:

1. Sugar Coating - Deposition of coating material onto the substrate from aqueous solution/suspension of coatings, based predominately upon sucrose as a raw material.
2. Film Coating - The deposition of polymeric film onto the solid dosage form.
3. Microencapsulation - The deposition of a coating material onto a particle, pellet, granule, or bead core. The substrate in this application ranges in size from submicron to several millimeters. It is this size range that differentiates it from the standard coating described in 1 and 2 above.
4. Compression Coating (This topic is addressed in the Unit Dosing section.)

b. Printing: The marking of a capsule or tablet surface for the purpose of product identification. Printing may be accomplished by either the application of a contrasting colored polymer (ink) onto the surface of a capsule or tablet, or by the use of laser etching.

The method of application, provided the ink formulation is not altered, is of no consequence to the physical-chemical properties of the product.

2. Operating Principles

a. Pan Coating

The uniform deposition of coating material onto the surface of a solid dosage form, or component thereof, while being translated via a rotating vessel.

b. Gas Suspension

The application of a coating material onto a solid dosage form, or component thereof, while being entrained in a process gas stream.

Alternatively, this may be accomplished simultaneously by spraying the coating material and substrate into a process gas stream.

c. Vacuum Film Coating

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.

d. Dip Coating

Coating is applied to the substrate by dipping it into the coating material. Drying is accomplished using pan coating equipment.

e. Electrostatic Coating

A strong electrostatic charge is applied to the surface of the substrate. The coating material containing oppositely charged ionic species is sprayed onto the substrate.

f. Compression Coating

Refer to the Unit Dosing section of this document.

g. Ink-Based Printing

The application of contrasting colored polymer (ink) onto the surface of a tablet or capsule.

h. Laser Etching

The application of identifying markings onto the surface of a tablet or capsule using laser-based technology.

B. Equipment Classification

1. Pan Coating

Pan coating subclasses primarily are distinguished by the pan configuration, the pan perforations, and/or the perforated device used to introduce process air for drying purposes. Perforated coating systems include both batch and continuous coating processes.

- Conventional Coating System
- Perforated Coating System

2. Gas Suspension

Gas suspension subclasses primarily are distinguished by the method by which the coating is applied to the substrate.

- Fluidized Bed
- Spray Congealing/Drying

3. Vacuum Film Coating

Although there may be differences in the jacketed pan, baffle system, or vacuum source, no vacuum film coating subclasses have been identified.

4. Dip Coating

Because of the custom design associated with this class of coating, no dip coating subclasses or examples have been identified.

5. Electrostatic Coating

Because of the custom design associated with this class of coating, no electrostatic coating subclasses or examples have been identified.

6. Compression Coating

Refer to the Unit Dosing section of this document.

7. Ink-Based Printing

Ink-based printing subclasses primarily are distinguished by the method by which the marking is applied to a capsule or tablet surface.

- Offset
- Ink Jet

8. Laser Etching (Printing)

Although laser etching systems may differ from one another, no laser etching subclasses have been identified.

Table 1 Unit Operation - Coating Equipment

Class	Subclass	Examples
Pan Coating	Conventional Coating System	Bruck O'Hara Pellegrini Stokes-Merrill
	Perforated Coating System	BWI Hüttlin (Thomas Engineering) Driam Glatt Nicomac O'Hara Raymond Strunck Thomas Engineering Vector
Gas Suspension	Fluidized Bed	Aeromatic-Fielder (GEA Niro) L.B. Bohle BWI Hüttlin (Thomas Engineering) Fluid Air Glatt Vector
	Spray Congealing/Drying	Allgaier APV BWI Hüttlin (Thomas Engineering) GEA-Niro Glatt
Vacuum Film Coating	None Identified	Glatt
Dip Coating	None Identified	None Identified
Electrostatic Coating	None Identified	None Identified

Table 2 Unit Operation - Printing Equipment

Class	Subclass	Examples
Ink-Based Printing	Off Set	Ackley Hartnett Markem Takeda
	Ink Jet	Image Linx
Laser Etching (Printing)	None Identified	Lumonics