Guidance for Industry

SUPAC: Manufacturing Equipment Addendum

DRAFT GUIDANCE

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

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CMC

Contains Nonbinding Recommendations

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Guidance for Industry

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Food and Drug Administration
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Guidance for Industry[1]
SUPAC: Manufacturing Equipment Addendum

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This draft guidance combines and supersedes the following scale-up and post-approval changes (SUPAC) guidances for industry: (1) *SUPAC-IR/MR: Immediate Release and Modified Release Solid Oral Dosage Forms, Manufacturing Equipment Addendum*, and (2) *SUPAC-SS Nonsterile Semisolid Dosage Forms, Manufacturing Equipment Addendum*.[2] It removes the lists of manufacturing equipment that were in both guidances and clarifies the types of processes being referenced.

This draft SUPAC addendum should be used in conjunction with the following SUPAC guidances for industry:[3] (1) *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*, (2) *SUPAC-MR: Modified Release Solid Oral Dosage Forms Scale-Up and Post-Approval Changes: Chemistry, Manufacturing and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation*, and (3) *SUPAC-SS: Nonsterile Semisolid Dosage Forms, Scale-Up and Post Approval Changes: Chemistry Manufacturing and Controls; In Vitro Release Testing and In Vivo Bioequivalence Documentation*.[4]

The SUPAC guidances define: (1) levels of chemistry, manufacturing, and control change; (2) recommended chemistry, manufacturing, and controls tests for each level of change; (3) recommended in vitro dissolution and release tests and/or in vivo bioequivalence tests for each level of change; and (4) recommended documentation that should support the change for new drug applications and abbreviated new drug applications.

[1] 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.

[2] For this guidance only, the new document that is a combination of these two guidances will be referred to as the *SUPAC addendum*.

[3] 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.

[4] For this guidance only, this collective group of guidances will be referred to as *SUPAC guidances*.

This draft SUPAC addendum, together with the SUPAC guidances, is intended to help you, the manufacturer, determine the documentation you should submit to FDA regarding manufacturing equipment changes.

FDA's guidance documents, including this guidance, do not establish legally enforceable 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.

II. BACKGROUND

When the SUPAC equipment addenda were published with tables referencing specific equipment, the tables were misinterpreted as equipment required by FDA. FDA recognizes that scientific innovation and technology advancement are commonplace and play a significant role in pharmaceutical development, manufacturing, and quality assurance, and we are concerned that such a misunderstanding could discourage advancements in manufacturing technologies. Therefore, this revised draft SUPAC addendum contains general information on SUPAC equipment and no longer includes tables referencing specific equipment. This draft guidance also includes changes to clarify the types of processes being referenced.

III. DISCUSSION

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

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 with the regulations, including the CGMP regulations.[5, 6] We also recommend addressing the impact on the product quality attributes of equipment variations (via process parameters) when designing and developing the manufacturing process.

When making equipment changes, you will need to determine the filing requirement.[7] The SUPAC guidances provide information on how to do so. FDA will assess the changes based on the types of equipment changes being considered. If you choose an approach that exceeds the SUPAC guidances and addendum, FDA will assess the changes provided they are supported by a suitable risk-based assessment.

[5] 21 CFR 314.70.
[6] 21 CFR 210-211.
[7] 21 CFR 314.70.

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 FDA review at its discretion.

IV. SUPAC IR/MR INFORMATION

A. Particle Size Reduction/Separation

1. Definitions

a. Unit Operations

i. 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.

a. Particle – Refers to either a discrete particle or a grouping of particles, generally know as an agglomerate.

b. 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.

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

b. Operating Principles

i. 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.

ii. Impact Milling

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

iii. Cutting

Particles are reduced in size by mechanical shearing.

iv. Compression Milling

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

v. Screening

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

vi. Tumble Milling

Particles are reduced in size by attrition utilizing grinding media.

vii. 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.

2. Equipment Classifications

a. 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
- High Pressure Homogenizer

b. 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

c. Cutting Mills

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

d. 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.

e. Screening Mills

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

- Rotating Impeller
- Rotating Screen
- Oscillating Bar

f. 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

g. Separators

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

- Vibratory/Shaker
- Centrifugal

B. Blending and Mixing

1. *Definitions*

a. Unit Operations

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

b. Operating Principles

i. 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.

ii. Convection Mixing

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

iii. Pneumatic Mixing

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

2. *Equipment Classifications*

a. 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

b. 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

c. 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.

C. Granulation

1. Definitions

a. 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.

b. Operating Principles

i. Dry Granulation

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

ii. 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.

iii. 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.

iv. 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.

v. Extrusion Granulation

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

vi. Rotary Granulation

Spheronization, agglomeration, and/or densification of a wetted or non-wetted powder or extruded material. This is accomplished by centrifugal or rotational forces from a central rotating disk, rotating walls, or both. The process may include the incorporation and/or drying of a granulation fluid.

vii. 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.

viii. 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.

ix. Hot-melt Granulation

An agglomeration process that utilizes a molten liquid as a binder(s) or granulation matrix in which the active pharmaceutical ingredient (API) is mixed and then cooled down followed by milling into powder. This is usually accomplished in a temperature controlled jacketed high shear granulating tank or using a heated nozzle that sprays the molten binders(s) onto the fluidizing bed of the API and other inactive ingredients.

2. Equipment Classification

a. Dry Granulator

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

- Slugging
- Roller Compaction

b. 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.

- Vertical (Top or Bottom Driven)
- Horizontal (Side Driven)

c. 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

d. 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.

- Slant cone
- Double cone
- V-blender

e. 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

f. Rotary Granulator

Rotary granulator subclasses primarily are distinguished by their structural architecture. They have either open top architecture, such as a vertical centrifugal spheronizer, or closed top architecture, such as a closed top fluid bed dryer.

- Open
- Closed

g. 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.

h. 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.

i. Hot-melt Granulator

Although, hot-melt granulator may differ from one another in primarily melting the inactive ingredient (particularly the binder or other polymeric matrices), no subclasses have been indentified yet.

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.

D. Drying

1. Definitions

a. Unit Operation

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

b. Operating Principles

i. 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.

ii. 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.

iii. 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.

iv. 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.

v. 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.

vi. 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.

vii. 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.

viii. Indirect Conduction, Lyophilization

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

ix. 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.

x. 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 another. This process commonly is referred to as microwave drying.

2. Equipment Classifications

a. 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

b. 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

c. 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.

d. 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.

e. 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.

f. 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

g. Indirect Conduction Heating, Static Solids Beds

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

h. Indirect Conduction, Lyophilization

No lyophilizer subclasses have been identified.

i. 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.

j. 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.

E. Unit Dosing

1. Definitions

a. Unit Operation

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

b. Operating Principles

i. Tabletting

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

ii. Encapsulating

The division of material 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.

iii. Powder Filling

The division of a powder blend into a container closure system.

2. Equipment Classifications

a. 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

Tablet press subclasses are also distinguished from one another for some special types of tablets where more than one hopper and precise powder feeding mechanism might be necessary.

- Micro/ mini tablet press
- Multi-layer tablet press (bi-layer, tri-layer)

b. Encapsulator

Encapsulator subclasses primarily are distinguished from one another by the method that is used for introducing material into the capsule. Encapsulators can deliver materials 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

c. Powder Filler

Subclasses of powder fillers primarily are distinguished by the method used to deliver the predetermined amount for container fill.

- Vacuum
- Auger

F. Soft Gelatin Capsule

1. Definitions

a. Unit Operations

i. 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.

ii. 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.

iii. 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.

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.

v. 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.

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

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

b. Operating Principles

i. 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.

ii. 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.[8]

iii. 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.

iv. 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.

v. Encapsulation

The formation of capsules using a rotary die machine.[9]

vi. Inspection/Sorting

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

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

[9] 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.

vii. 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.

2. Equipment Classifications

a. 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

b. Deaggregators

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

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

c. 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

d. 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 been identified.

- Jacketed vessel with and without mixing system

e. Encapsulators

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

- Positive Displacement Pump
- Gravity or Force Fed

f. 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

G. Coating/Printing/Drilling

1. *Definitions*

a. Unit Operation

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

a. Protect the drug from its surrounding environment (air, moisture, and light), with a view to improving stability.
b. Mask unpleasant taste, odor, or color of the drug.
c. Increase the ease of ingesting the product for the patient.
d. Impart a characteristic appearance to the tablets, which facilitates product identification and aids patient compliance.
e. Provide physical protection to facilitate handling. This includes minimizing dust generation in subsequent unit operations.
f. Reduce the risk of interaction between incompatible components. This would be achieved by coating one or more of the offending ingredients.

g. Modify the release of drug from the dosage form. This includes delaying, extending, and sustaining drug substance release.

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

a. Sugar Coating - Deposition of coating material onto the substrate from aqueous solution/suspension of coatings, based predominately upon sucrose as a raw material.
b. Film Coating - The deposition of polymeric film onto the solid dosage form.
c. Core Enrobing - The gelatin coating of gravity or force fed pre- formed tablets or caplets.
d. 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.
e. Compression Coating (This topic is addressed in the Unit Dosing section.)

ii. 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.

iii. Drilling: The drilling or ablating of a hole or holes through the polymeric film coating shell on the surfaces of a solid oral dosage form using a laser. The polymeric film shell is not soluble in vivo. The hole or holes allow for the modified release of the drug from the core of the dosage form.

b. Operating Principles

i. 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.

ii. 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.

iii. 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.

iv. Dip Coating

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

v. 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.

vi. Compression Coating

Refer to the Unit Dosing section of this document.

vii. Ink-Based Printing

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

viii. Laser Etching

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

ix. Drilling

A drilling system typically is a custom built unit consisting of a material handling system to orient and hold the solid dosage form, a laser (or lasers), and optics (lenses, mirrors, deflectors, etc.) to ablate the hole or holes, and controls. The drilling unit may include debris extraction and inspection systems as well. The sorting, orienting, and holding equipment commonly is provided by dosage form printing equipment manufacturers, and is considered ancillary in this use.

2. Equipment Classification

a. 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

b. Gas Suspension

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

- Fluidized Bed with bottom spray mechanism
- Fluidized Bed with tangential spray mechanism
- Fluidized Bed with top spray mechanism
- Fluidized Bed with Wurster column
- Spray Congealing/Drying

c. 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.

d. Dip Coating

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

e. Electrostatic Coating

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

f. Compression Coating

Refer to the Unit Dosing section of this document.

g. 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

h. Laser Etching (Printing)

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

i. Drilling

The method of producing the laser pulse that ablates the hole(s) is of no consequence to the physical-chemical properties of the product. Therefore, no dosage form drilling equipment subclasses have been identified.

V. SUPAC-SS INFORMATION

A. Particle Size Reduction/Separation

1. Definitions

a. Unit Operations

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

a. Particle - Either a discrete particle or a grouping of particles, generally known as an agglomerate.

b. Particle Size Reduction Mechanisms

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

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

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

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

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

b. Operating Principles

i. Fluid Energy Milling: Particle size reduction by high-speed particle-to- particle impact and/or attrition (also known as micronizing).

ii. Impact Milling**:** Particle size reduction by high-speed mechanical impact or impact with other particles (also known as milling, pulverizing, or comminuting).

iii. Cutting: Particle size reduction by mechanical shearing.

iv. Compression Milling: Particle size reduction by compression stress and shear between two surfaces.

v. Screening: Particle size reduction by mechanically-induced attrition through a screen (commonly referred to as milling or deagglomeration).

vi. Tumble Milling: Particle size reduction by attrition, using grinding media.

vii. Separating: Particle segregation based on size alone, without any significant particle size reduction (commonly referred to as screening or bolting).

2. Equipment Classifications

a. Fluid Energy Mills

Fluid energy mill subclasses have no moving parts and primarily differ in the configuration and/or shape of their chambers, nozzles, and classifiers.

- Fixed target
- Fluidized bed
- Loop and/or oval

- Moving target
- Opposed jet
- Opposed jet with dynamic classifier
- Tangential jet

b. Impact Mills

Impact mill subclasses primarily differ in the configuration of the grinding heads, chamber grinding liners (if any), and classifiers.

- Cage
- Hammer air swept
- Hammer conventional
- Pin or disc

c. Cutting Mills

Although cutting mills can differ in whether the knives are movable or fixed, and in classifier configuration, no cutting mill subclasses have been identified.

d. Compression Mills

Although compression mills, also known as roller mills, can differ in whether one or both surfaces move, no compression mill subclasses have been identified.

e. Screening Mills

Screening mill subclasses primarily differ in the rotating element.

- Oscillating bar
- Rotating impeller
- Rotating screen

f. Tumbling Mills

Tumbling mill subclasses primarily differ in the grinding media used and whether the mill is vibrated.

- Ball media
- Rod media
- Vibrating

g. Separators

Separator subclasses primarily differ in the mechanical means used to induce particle movement.

- Centrifugal
- Vibratory or shaker

Note: If a single piece of equipment is capable of performing multiple discrete unit operations, it has been evaluated solely for its ability to impact particle size or separation.

B. Mixing

1. Definitions

a. Unit Operation

Mixing: The reorientation of particles relative to one another to achieve uniformity or randomness. This process can include wetting of solids by a liquid phase, dispersion of discrete particles, or deagglomeration into a continuous phase. Heating and cooling via indirect conduction may be used in this operation to facilitate phase mixing or stabilization.

b. Operating Principles

i. Convection Mixing, Low Shear: Mixing process with a repeated pattern of cycling material from top to bottom, in which dispersion occurs under low power per unit mass through rotating low shear forces.

ii. Convection Mixing, High Shear: Mixing process with a repeated pattern of cycling material from top to bottom, in which dispersion occurs under high power per unit mass through rotating high shear forces.

iii. Roller Mixing (Milling): Mixing process by high mechanical shearing action where compression stress is achieved by passing material between a series of rotating rolls. This is commonly referred to as compression or roller milling.

iv. Static Mixing: Mixing process in which material passes through a tube with stationary baffles. The mixer is generally used in conjunction with an in-line pump.

2. Equipment Classification

a. Convection Mixers, Low Shear

This group normally operates under low shear conditions and is broken down by impeller design and movement. Design can also include a jacketed vessel to facilitate heat transfer.

- Anchor or sweepgate
- Impeller
- Planetary

b. Convection Mixers, High Shear

This group normally operates only under high shear conditions. Subclasses are differentiated by how the high shear is introduced into the material, such as by a dispersator with serrated blades or homogenizer with rotor stator.

- Dispersator
- Rotor stator

c. Roller Mixers (Mills)

No roller mixer subclasses have been identified.

d. Static Mixers

No static mixer subclasses have been identified.

Note: If a single piece of equipment is capable of performing multiple discrete unit operations, it has been evaluated solely for its ability to mix materials.

C. Emulsification

1. Definitions

a. Unit Operation

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.

b. Operating Principles

i. Low Shear Emulsification: Use of low shear energy using mechanical mixing with an impeller to achieve a dispersion of the mixture. The effectiveness of this operation is especially dependent on proper formulation.

ii. High Shear Emulsification: Use of high shear energy to achieve a dispersion of the immiscible phases. High shear can be achieved by the following means:

a. Stirring the mixture with a high speed chopper or saw-tooth dispersator.

b. Passing the mixture through the gap between a high-speed rotor and a stationary stator.

c. Passing the mixture through a small orifice at high pressure (valve- type homogenizer) or through a small orifice at high pressure followed by impact against a hard surface or opposing stream (valve-impactor type homogenizer), causing sudden changes of pressure.

2. Equipment Classification

a. Low Shear Emulsifiers

Although low shear emulsification equipment (mechanical stirrers or impellers) can differ in the type of fluid flow imparted to the mixture (axial-flow propeller or radial-flow turbines), no subclasses have been defined.

b. High Shear Emulsifiers

Subclasses of high shear emulsification equipment differ in the method used to generate high shear.

- Dispersator
- Rotor stator
- Valve or pressure homogenizer

Note: If a single piece of equipment is capable of performing multiple discrete unit operations, the unit has been evaluated solely for its ability to emulsify materials.

D. Deaeration

1. Definitions

a. Unit Operation

Deaeration: The elimination of trapped gases to provide more accurate volumetric measurements and remove potentially reactive gases.

b. Operating Principles

The use of vacuum or negative pressure, alone or in combination with mechanical intervention or assistance.

2. Equipment Classification

a. Deaerators

Deaerator subclasses differ primarily in their air removal paths, either through the bulk material or through a thin film, and in whether they use a batch or in-line process.

- Off-Line or in-line
- Vacuum vessel

Note: If a single piece of equipment is capable of performing multiple discrete unit operations, it has been evaluated solely for its ability to deaerate materials.

E. Transfer

1. Definition

a. Unit Operation

Transfer: The controlled movement or transfer of materials from one location to another.

b. Operating Principles

i. Passive: The movement of materials across a non-mechanically-induced pressure gradient, usually through conduit or pipe.

ii. Active: The movement of materials across a mechanically-induced pressure gradient, usually through conduit or pipe.

2. Equipment Classification

a. Low Shear

Active or passive material transfer, with a low degree of induced shear

- Diaphragm
- Gravity
- Peristaltic
- Piston
- Pneumatic
- Rotating lobe
- Screw or helical screw

b. High Shear

Active or mechanical material transfer with a high degree of induced shear

- Centrifugal or turbine
- Piston
- Rotating gear

Note: This section is intended to deal with the transfer of shear sensitive materials, including product or partially manufactured product. A single piece of equipment can be placed in either a low or high shear class, depending on its operating parameters. If a single piece of equipment is capable of performing multiple discrete unit operations, the unit has been evaluated solely for its ability to transfer materials.

F. Packaging

1. Definitions

a. Unit Operation

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 product to primary pack containers

iv. Sealing: A device or process for closing and/or sealing primary pack containers following the filling process.

b. Operating Principles

i. Holding: The storage of liquid, semi-solids, or product 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.

iv. Sealing: Primary packages can be sealed using a variety of methods, including conducted heat and electromagnetic (induction or microwave) or mechanical manipulation (crimping or torquing).

2. Equipment Classification

a. Holders

Although holding vessels can differ in their geometry and ability to control temperature or agitation, their primary differences are based on how materials are fed.

- Auger
- Gravity
- Pneumatic (nitrogen, air, etc.)

b. Fillers

The primary differences in filling equipment are based on how materials are metered.

- Auger
- Gear pump
- Orifice
- Peristaltic pump
- Piston

c. Sealers

The differences in primary container sealing are based on how energy is transferred or applied.

- Heat
- Induction
- Microwave
- Mechanical or crimping
- Torque