Guidance for Industry

SUPAC-SS: Nonsterile Semisolid Dosage Forms

Manufacturing Equipment Addendum

DRAFT GUIDANCE

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For questions on the content of the draft document contact Nancy Sager, 301-594-5633 (CDER).

U.S. Department of Health and Human Services
Food and Drug Administration
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DRAFT - NOT FOR IMPLEMENTATION

GUIDANCE FOR INDUSTRY [1]

SUPAC-SS: Nonsterile Semisolid Dosage Forms Manufacturing Equipment Addendum

I. INTRODUCTION

This guidance is intended to provide recommendations to pharmaceutical manufacturers using the Center for Drug Evaluation and Research's guidance for industry, *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* (SUPAC-SS), which published in June 1997. This document should be used in conjunction with the SUPAC-SS guidance document in determining what documentation should be submitted to the Food and Drug Administration (FDA) on equipment changes made in accordance with the recommendations of the SUPAC-SS guidance document. The earlier SUPAC guidance document defines (1) levels of change; (2) recommended chemistry, manufacturing, and controls tests for each level of change; (3) recommended in vitro release tests and/or in vivo bioequivalence tests to support each level of change; and (4) documentation that should support the change for new drug applications (NDAs) and abbreviated new drug applications (ANDAs).

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. This 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, please contact the appropriate reviewing office at CDER.

Although this guidance does not discuss validation, any equipment changes should be validated in accordance with current good manufacturing practices (CGMPs). The resulting data will be subject to examination by field investigators during routine GMP inspections. The information here is presented in broad categories of unit operation (particle size reduction and/or separation, mixing, emulsification, deaeration, transfer, and packaging). Definitions and classifications are

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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-SS. 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.

provided. For each operation, a table categorizes equipment by class (operating principle) and subclass (design characteristic). Examples are given within the subclasses.

Under SUPAC-SS, equipment within the same class and subclass are considered to have the same design and operating principle. For example, a change from a planetary mixer from manufacturer A to another planetary mixer from manufacturer B would not represent a change in design or operating principle and would be considered the same.

A 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 planetary mixer to a dispersator mixer demonstrates a change in operating principle from low-shear convection mixing to high-shear convection mixing. These types of equipment would be considered different under SUPAC-SS.

Applicants should carefully consider and evaluate on a case-by-case basis changes in equipment that are in the same class, but different subclasses.[2] In many situations, these changes in equipment would be considered similar. For example, in Section III, Mixing, under the convection mixers, low shear, a change from an impeller mixer (subclass) to a planetary mixer (subclass) represents a change within a class and between subclasses. Provided the manufacturing process with the new equipment is validated, this change would likely not need a changes being effected (CBE) supplement. At the time of such a change the applicant should have available the scientific data and rationale used to make this determination. It is up to the applicant to determine the filing category.

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

On November 21, 1997, the President signed the Food and Drug Administration Modernization Act (FDAMA).[3] Section 116 of FDAMA amended the Food, Drug, and Cosmetic Act by adding section 506A (21 U.S.C. 356a), which provides requirements for making and reporting

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[2] In the guidance for industry, *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* (SUPAC-SS), a changes being effected (CBE) supplement is recommended for a change in equipment to a "different design ***or*** operating principle." On further review, CDER has determined this should state "different design ***and*** operating principle." The SUPAC-SS guidance will be revised to make this change after the comment period closes on this Addendum and it is finalized.

[3] Pub. L. 105-115

manufacturing changes to an approved human and animal drug application and for distributing a drug product made with such change. The FDA is currently preparing a proposed rule to amend its regulations (21 CFR 314.70 and 21 CFR 514.8) for supplements and other changes to approved applications to implement the manufacturing changes provision of FDAMA. This draft guidance will be revised as and when appropriate to take into consideration the revised regulations in 21 CFR 314.70 and 21 CFR 514.8 when they are finalized.

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 size reduction mechanisms. The mechanical process used is generally referred to as milling.

      i. Particle - 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 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

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

2. Operating Principles

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

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

c. Cutting: Particle size reduction by mechanical shearing

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

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

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

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

B. Equipment Classifications

1. 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

2. 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

3. 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.

4. 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.

5. Screening Mills

   Screening mill subclasses primarily differ in the rotating element.

   - Oscillating bar
   - Rotating impeller
   - Rotating screen

6. Tumbling Mills

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

   - Ball media
   - Rod media
   - Vibrating

7. 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.

Table 1 Unit Operation - Particle Size Reduction

Class	Subclass	Examples
Fluid Energy Mills	Fixed Target	None Identified
	Fluidized Bed	None Identified
	Loop/Oval	Fluid Energy Aljet
	Moving Target	None Identified
	Opposed Jet	Garlock
	Opposed Jet with Dynamic Classifier	Alpine (Hosokawa) Fluid Energy Aljet
	Tangential Jet	Alpine (Hosokawa) Fluid Energy Aljet Sturtevant
Impact Mills	Cage	Stedman
	Hammer Air Swept	Alpine (Hosokawa) Bepex (Hosowaka) Sturtevant
	Hammer Conventional	Alpine (Hosokawa) Fitzpatrick Fluid Air Mikro (Hosokawa) Rietz (Hosokawa) Stokes-Merrill
	Pin/Disc	Alpine (Hosokawa) Kemutec Sturtevant
Cutting Mills	None Identified	Alpine (Hosokawa) Fitzpatrick Urschel
Compression Mills	None Identified	MCA International Ross Stokes-Merrill
Screening Mills	Oscillating Bar	Bepex (Hosokawa) Frewitt Jackson-Crockatt Stokes-Merrill Vector
	Rotating Impeller	Bepex (Hosokawa) Fitzpatrick Fluid Air Kemutec Quadro Stokes-Merrill Zanchetta (Romaco)
	Rotating Screen	Glatt
Tumbling Mills	Ball Media	US Stoneware
	Rod Media	None Identified
	Vibrating	Sweco

Table 2 Unit Operation - Separation

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

III. MIXING

A. Definitions

1. 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.

2. Operating Principles

a. 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

b. 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

c. 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.

d. 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.

B. Equipment Classification

1. 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

2. 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

3. Roller Mixers (Mills)

No roller mixer subclasses have been identified.

4. 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.

Table 3 Unit Operation - Mixing

Class	Subclass	Examples
Convection Mixers, Low Shear	Anchor/Sweepgate	Brogli Fryma GEI Krieger (GEI North America) Groen Koruma (Romaco) Lee Industries Ross Waukesha Cherry Burrell
	Impeller	Bematek Chemineer Gate IKA Lightnin Moorhouse-Cowles Quadro Ross
	Planetary	Aaron Aeschbach AMF GEI-Collette (GEI North America/Vector) Hobart Jaygo Littleford Day Ross Vrieco
Convection Mixers, High Shear	Dispersator	Chemineer Cowles Gate IKA Koruma (Romaco) Lightnin Ross
	Roto Stator	Arde-Barinco Bematek Fryma Gaulin Greerco Koruma (Romaco) Manton Gaulin Moorhouse-Cowles Premier Ross Silverson Tri-Homo Ultra Turex Urschel

Table 3 Unit Operation - Mixing (cont.)

Class	Subclass	Examples
Roller Mixers (Mills)	None Identified	MCA International Ross Stokes Merrill
Static Mixers	None Identified	Ross

IV. EMULSIFICATION

A. Definitions

1. 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.

2. Operating Principles

a. 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.

b. 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:

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

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

iii. 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

B. Equipment Classification

1. 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.

2. 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.

Table 4 Unit Operation - Emulsification

Class	Subclass	Examples
Low Shear Emulsifiers	None Identified	Bematek Lightnin Moorhouse-Cowles Ross
High Shear Emulsifiers	Dispersator	Chemineer Cowles Gate IKA Koruma (Romaco) Lightnin Ross
	Rotor Stator	Arde-Barinco Bematek Fryma Gaulin Greerco Koruma (Romaco) Manton Gaulin Moorhouse-Cowles Premier Ross Silverson Tri-Homo Ultra Turex Urschel
	Valve or Pressure Homogenizer	Manton Gaulin Microfluidics

V. DEAERATION

A. Definitions

1. Unit Operation

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

2. Operating Principles

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

B. Equipment Classification

1. 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.

Table 5 Unit of Operation - Deaeration

Class	Subclass	Examples
Deaerators	Off Line/In Line	Cornell Machine Co. Fryma Jaygo Koruma (Romaco)
	Vacuum Vessel	Fryma GEI-Kreiger (GEI North America) Groen Koruma (Romaco) Lee Industries Paul Mueller Co.

VI. TRANSFER

A. Definition

1. Unit Operation

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

2. Operating Principles

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

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

B. Equipment Classification

1. 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

2. 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.

Table 6 Unit Operation - Transfer

Class	Subclass	Examples
Low Shear	Diaphragm	APV Pulsafeeder TL Systems Tri-Clover Wilden
	Gravity	None Identified
	Peristaltic	Barnant Co Cole Palmer Pulsafeeder Vanton Watson-Marlow
	Piston	APV Graco National Nordson Waukesha Wilden
	Pneumatic	None Identified
	Rotating Lobe	Flowteck Fristam Sine Tri-Clover Viking Waukesha
	Screw or Helical Screw	Moyno
High Shear	Centrifugal or Turbine	APV BMS Fristam Pulsafeeder Tri-Clover Vanton Waukesha
	Piston	APV Graco National Instrument Nordson Waukesha Wilden
	Rotating Gear	APV BSM Ertel Engineering Pulsafeeder Viking Waukesha

VII. PACKAGING

A. Definitions

1. Unit Operation

   a. Holding: The process of storing product after completion of manufacturing process and prior to filling final primary packs

. b. Transfer: The process of relocating bulk finished product from holding to filling equipment using pipe, hose, pumps and/or other associated components

   c. Filling: The delivery of target weight or volume of bulk finished product to primary pack containers

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

2. Operating Principles

   a. Holding: The storage of liquid, semi-solids, or product materials in a vessel that may or may not have temperature control and/or agitation

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

   c. 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.

   d. 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).

B. Equipment Classification

1. 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.)

2. Fillers

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

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

3. Sealers

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

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

Table 7 Unit Operation - Holding

Class	Subclass	Examples
Holders	Auger	Bonafacci Bosch Cozzoli Machine Erweka Fryma-Maschinenbau Inova Loeb Equipment Sarong Young Industries
	Gravity	Bonafacci Bosch Cozzoli Machine Erweka Fryma-Maschinenbau Inova Loeb Equipment Sarong Young Industries
	Pneumatic (nitrogen, air, etc.)	Bonafacci Bosch Cozzoli Machine Erweka Fryma-Maschinenbau Inova Loeb Equipment Sarong Young Industries

Table 8 Unit Operation - Filling

Class	Subclass	Examples
Fillers	Auger	Bonafacci Bosch Erweka Fryma-Maschinenbau IWKA Kalish Norden Sarong
	Gear pump	APV BMS Bonafacci Bosch Ertel Engineering Erweka Fryma-Maschinenbau IWKA Kalish Norden Pulsafeeder Sarong Viking Waukesha
	Orifice	Bonafacci Bosch Erweka Fryma-Maschinenbau IWKA Kalish Norden Sarong
	Peristaltic pump	Barnant Co. Bonafacci Bosch Cole-Parmer Erweka Fryma-Maschinenbau IWKA Kalish Norden Pulsafeeder Sarong Vanton Watson-Marlow

Table 8 Unit Operation - Filling (cont.)

Class	Subclass	Examples
Fillers (cont..)	Piston	APV Bonafacci Bosch Erweka Fryma-Maschinenbau Graco IWKA Kalish National Norden Sarong Waukesha Wilden

Table 9 Unit Operation - Sealing

Class	Subclass	Examples
Sealers	Heat	Harro Höfliger Packaging Hutchins and Hutchins Loeb Equipment Prodo-Pak Romaco VWR Scientific Products
	Induction	Pillar
	Microwave	None Identified
	Mechanical/Crimping	Austin Reed Bishop International Chase-Logeman Cozzoli Machine Integrated Packaging System Loeb Equipment Romaco VWR Scientific Products
	Torque	Bausch and Stroebel Machine Cozzoli Machine Electronic Liquid Filler Madison Equipment Sure Torque