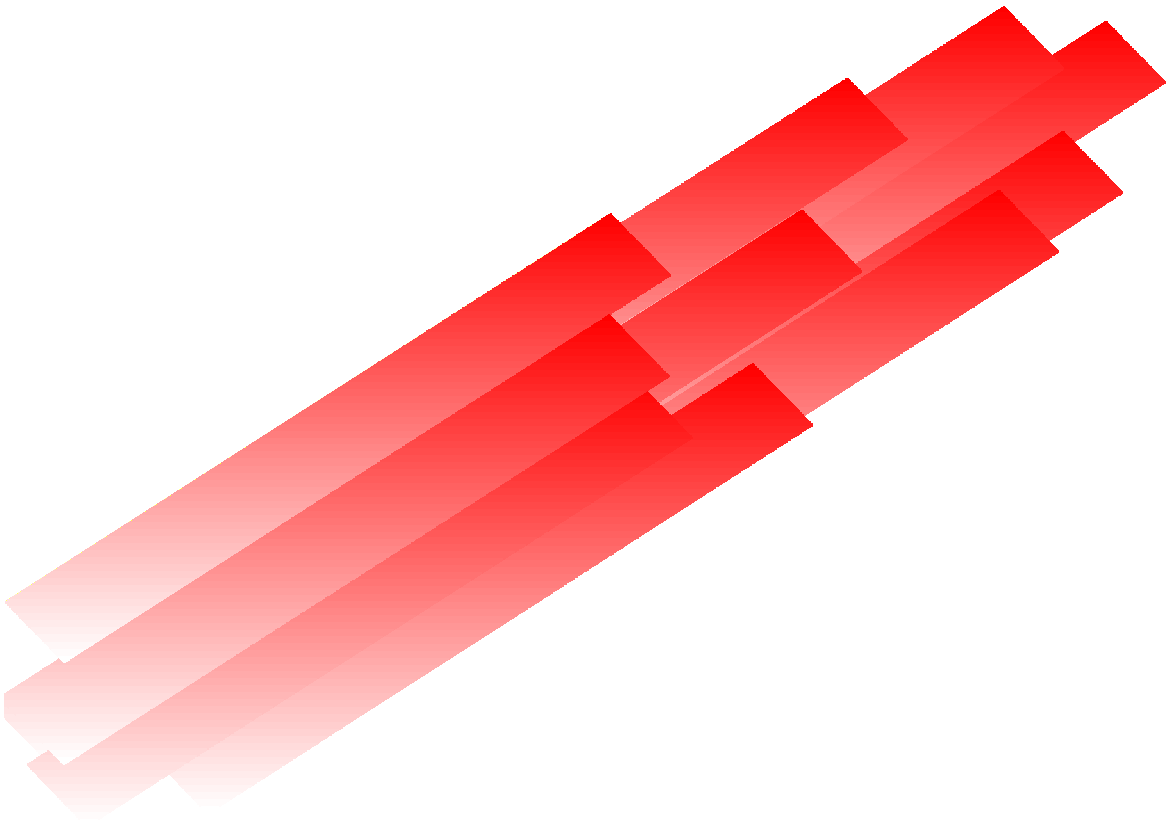
Guidance for Industry

SUPAC-MR: Modified Release Solid Oral Dosage Forms

Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
September 1997
CMC 8

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I. INTRODUCTION

This guidance provides recommendations to pharmaceutical sponsors of new drug applications (NDAs), abbreviated new drug applications (ANDAs), and abbreviated antibiotic drug applications (AADAs) who intend to change (1) the components or composition, (2) the site of manufacture, (3) the scale-up/scale-down of manufacture, and/or (4) the manufacturing (process and equipment) of a modified release solid oral dosage form during the postapproval period.

The guidance defines (1) levels of change, (2) recommended chemistry, manufacturing, and controls (CMC) tests for each level of change, (3) recommended in vitro dissolution tests and/or in vivo bioequivalence tests for each level of change; and (4) documentation that should support the change. This guidance specifies application information that should be provided to the Center for Drug Evaluation and Research (CDER) to ensure continuing product quality and performance characteristics of a modified release solid oral dose formulation for specified postapproval changes.

This guidance does not comment on or otherwise affect compliance/inspection documentation that has been defined by CDER's Office of Compliance or FDA's Office of Regulatory Affairs. This guidance does not affect any postapproval changes other than the ones specified. For those changes filed in a Changes Being Effected (CBE) supplement (21 CFR 314.70(c)), the FDA may, after a review of the supplemental information, decide that the changes are not approvable. For changes not addressed in this guidance, or for multiple changes submitted at one time or over a short period of time, sponsors should contact the appropriate CDER review division or consult other CDER guidances to obtain information about tests and application documentation.

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[1]This guidance has been prepared by the Scale-up and Postapproval Change Modified Release (SUPAC-MR) Working Group operating under the direction of the Chemistry Manufacturing Controls Coordinating Committee (CMC CC) and the Biopharmaceutics Coordinating Committee (BCC) in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA). This guidance represents the Agency's current thinking on modified release solid oral dosage forms scale-up and postapproval changes. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirement of the applicable statute, regulations, or both.

FDA regulations at 21 CFR 314.70(a) provide that applicants may make changes to an approved application in accordance with a guidance, notice, or regulation published in the *Federal Register* that provides for a less burdensome notification of the change (for example, by notification at the time a supplement is submitted or in the next annual report). This guidance permits less burdensome notice of certain postapproval changes within the meaning of § 314.70(a).

For postapproval changes for modified release solid oral dosage forms that affect components and composition, scale-up/scale-down, site change, and manufacturing process or equipment changes, this guidance supersedes the recommendations in section 4.G of the Office of Generic Drugs (OGD) Policy and Procedure Guide 22-90 (September 11, 1990). For all other dosage forms and changes, this guidance does not affect the recommendations in Guide 22-90.

II. GENERAL STABILITY CONSIDERATIONS

The effect SUPAC-type changes have on the stability of the drug product should be evaluated. For general guidance on conducting stability studies, applicants are referred to the FDA *Guideline for Submitting Documentation for the Stability of Human Drugs and Biologics (02/87)*. For SUPAC submissions, the following points also should be considered:

- In most cases (except those involving scale up), stability data from pilot scale batches will be acceptable to support the proposed change.

- Where stability data show a trend toward potency loss or degradant increase under accelerated conditions, it is recommended that historical accelerated stability data from a representative prechange batch be submitted for comparison. It is also recommended that under these circumstances, all available long-term data on test batches from ongoing studies be provided in the supplement. Submission of historical accelerated and available long-term data would facilitate review and approval of the supplement.

- A commitment should be included to conduct long-term stability studies through the expiration dating period, according to the approved protocol, on the first or first three (see text for details) production batches and to report the results in the annual reports.

III. COMPONENTS AND COMPOSITION — NONRELEASE CONTROLLING EXCIPIENT

This section of the guidance focuses on changes in nonrelease controlling excipients in the drug product. For modified release solid oral dosage forms, consideration should be given as to whether the excipient is critical or not critical to drug release. The sponsor should provide appropriate justifications for claiming any excipient(s) as a nonrelease controlling excipient in the formulation of the modified release solid oral dosage form. The functionality of each excipient

should be identified. Changes in the amount of the drug substance are not addressed by this guidance. Changes in components or composition that have the effect of adding a new excipient or deleting an excipient are defined at level 3 (defined below), except as described below in Section III.A.1.a. Waiver of bioequivalence testing for a change in composition which involves only a different color, flavor or preservative may be permissible as described in 21 CFR 320.22(d)(4).

A. Level 1 Change

1. Definition of Level

Level 1 changes are those that are unlikely to have any detectable impact on formulation quality and performance.

Examples:

a. Deletion or partial deletion of an ingredient intended to affect the color or flavor of the drug product; or change in the ingredient of the printing ink to another approved ingredient.

b. Changes in nonrelease controlling excipients, expressed as percentage (w/w) of total formulation, less than or equal to the following percent ranges:

Nonrelease Controlling Excipient	**Percent Excipient (w/w) Out Of Total Target Dosage Form Weight**
Filler	±5
Disintegrant	
Starch	±3
Other	±1
Binder	±0.5
Lubricant	
Ca or Mg Stearate	±0.25
Other	±1
Glidant	
Talc	±1
Other	±0.1
Film Coat	±1

These percentages are based on the assumption that the drug substance in the product is formulated to 100% of label/potency. The total additive effect of all

nonrelease controlling excipient changes should not be more than 5%.[2] The total weight of the dosage form should still be within the original approved application range.

The components (active and excipients) in the formulation should have numerical targets that represent the nominal composition of the drug product on which any future changes in the composition of the product are to be based. Allowable changes in the composition should be based on the original approved target composition and not on previous level 1 changes in the composition. For products approved with only a range for excipients, the target value may be assumed to be the midpoint of the original approved application range.

2. Test Documentation

a. Chemistry documentation
Application/compendial product release requirements.

Stability: First production batch on long-term stability data reported in annual report.

b. Dissolution documentation
None beyond application/compendial requirements.

c. Bioequivalence documentation
None.

3. Filing Documentation

Annual report (all information including long-term stability data).

B. Level 2 Change

1. Definition of Level

Level 2 changes are those that could have a significant impact on formulation quality and performance.

[2]Example: In a product consisting of active ingredient A, lactose, microcrystalline cellulose, and magnesium stearate, the lactose and microcrystalline cellulose should not vary by more than an absolute total of 5% (e.g., lactose increases by 2.5% and microcrystalline cellulose decreases by 2.5%) relative to the target dosage form weight if it is to stay within the level 1 range.

Examples:

a. A change in the technical grade and/or specifications of a nonrelease controlling excipient.[3]

b. Changes in nonrelease controlling excipients, expressed as percentage (w/w) of total formulation, greater than those listed above for a level 1 change, but less than or equal to the following percent ranges (which represent a two-fold increase over level 1 changes):

Nonrelease Controlling Excipient	**Percent Excipient (w/w) Out Of Total Target Dosage Form Weight**
Filler	±10
Disintegrant	
Starch	±6
Other	±2
Binder	±1
Lubricant	
Ca or Mg Stearate	±0.5
Other	±2
Glidant	
Talc	±2
Other	±0.2
Film Coat	±2

These percentages are based on the assumption that the drug substance in the drug product is formulated to 100% of label/potency. The total additive effect of all nonrelease controlling excipient changes should not change by more than 10%. The total weight of the dosage form could still be within or outside the original approved application range.

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The components (active and excipients) in the formulation should have numerical targets that represent the nominal composition of the product on which any future changes in the composition of the product are to be based. Allowable changes in the composition are based on the original approved target composition and not on the composition based on previous level 1 or level 2 changes. For products approved with only a range for excipients, the target value may be assumed to be the midpoint of the original approved application range.

[3]Example: Avicel PH102 vs. Avicel PH200

2. Test documentation

a. Chemistry documentation

Application/compendial product release requirements and updated executed batch records.

Stability: One batch with three months accelerated stability data reported in prior approval supplement and long-term stability data of first production batch reported in annual report.

b. Dissolution documentation

Extended release: In addition to application/compendial release requirements, multipoint dissolution profiles should be obtained in three other media, for example, in water, 0.1N HCl, and USP buffer media at pH 4.5, and 6.8 for the changed drug product and the biobatch or marketed batch (unchanged drug product). Adequate sampling should be performed, for example, at 1, 2, and 4 hours and every two hours thereafter until either 80% of the drug from the drug product is released or an asymptote is reached. A surfactant may be used with appropriate justification.

Delayed release: In addition to application/compendial release requirements, dissolution tests should be performed in 0.1 N HCl for 2 hours (acid stage) followed by testing in USP buffer media, in the range of pH 4.5-7.5 (buffer stage) under standard (application/compendial) test conditions and two additional agitation speeds using the application/ compendial test apparatus (three additional test conditions). If the application/compendial test apparatus is the rotating basket method (Apparatus 1), a rotation speed of 50, 100, and 150 rpm may be used, and if the application/compendial test apparatus is the rotating paddle method (Apparatus 2), a rotation speed of 50, 75, and 100 rpm may be used. Multipoint dissolution profiles should be obtained during the buffer stage of testing. Adequate sampling should be performed, for example, at 15, 30, 45, 60, and 120 minutes (following the time from which the dosage form is placed in the buffer) until either 80% of the drug from the drug product is released or an asymptote is reached. The above dissolution testing should be performed using the changed drug product and the biobatch or marketed batch (unchanged drug product).

All modified release solid oral dosage forms: In the presence of an established in vitro/in vivo correlation (6), only application/compendial dissolution testing need be performed (i.e., only in vitro release data by the

correlating method need to be submitted). The dissolution profiles of the changed drug product and the biobatch or marketed batch (unchanged drug product) should be similar. The sponsor should apply appropriate statistical testing with justifications (e.g., the f_2 equation) for comparing dissolution profiles (5). Similarity testing for the two dissolution profiles (i.e., for the unchanged drug product and the changed drug product) obtained in each individual medium is appropriate.

c. Bioequivalence documentation

None.

3. Filing Documentation

Prior approval supplement (all information including accelerated stability data); annual report (long-term stability data).

C. Level 3 Change

1. Definition of Level

Level 3 changes are those that are likely to have a significant impact on formulation quality and performance.

Example:

a. Changes in the nonrelease controlling excipient range beyond those listed in Section III.B.1.b. The total weight of the dosage form may be within or outside the approved original application range.

2. Test Documentation

a. Chemistry documentation

Application/compendial product release requirements and updated executed batch records.

Stability:

Significant body of information available: One batch with three months' accelerated stability data reported in prior approval supplement and long-term stability data of first three production batches reported in annual report.

Significant body of information not available: Three batches with three months' accelerated stability data reported in prior approval supplement and long-term stability data of first three production batches reported in annual report.

b. Dissolution documentation

Extended release: In addition to application/compendial release requirements, a multipoint dissolution profile should be obtained using the application/compendial test conditions for the changed drug product and the biobatch or marketed batch (unchanged drug product). Adequate sampling should be performed, for example, at 1, 2, and 4 hours and every two hours thereafter, until either 80% of the drug from the drug product is released or an asymptote is reached.

Delayed release: In addition to application/compendial release requirements, a multipoint dissolution profile should be obtained during the buffer stage of testing using the application/compendial test conditions for the changed drug product and the biobatch or marketed batch (unchanged drug product). Adequate sampling should be performed, for example at 15, 30, 45, 60, and 120 minutes (following the time from which the dosage form is placed in the buffer) until either 80% of the drug from the drug product is released or an asymptote is reached.

c. Bioequivalence documentation

A single-dose bioequivalence study (3). The bioequivalence study may be waived in the presence of an established in vitro/in vivo correlation (6).

3. Filing Documentation

Prior approval supplement (all information including accelerated stability data); annual report (long-term stability data).

IV. COMPONENTS AND COMPOSITION — RELEASE CONTROLLING EXCIPIENT

This section of the guidance focuses on changes in release controlling excipients in the drug product. For modified release solid oral dosage forms, consideration should be given as to whether or not the excipient is critical to drug release. The sponsor should provide appropriate justifications (i.e., mechanism of drug release and manufacturing process) for claiming any excipient(s) as a release controlling excipient in the formulation of the modified release solid oral

dosage form. The functionality of each excipient should be identified. Changes in the amount of the drug substance are not addressed by this guidance. Changes exceeding the ranges defined in each of the levels below may be allowed if considered to be within normal batch-to-batch variation and contained within an approved original application. In such situations, sponsors should contact the appropriate CDER review division for further guidance.

A. Level 1 Change

1. Definition of Level

Level 1 changes are those that are unlikely to have any detectable impact on formulation quality and performance.

Example:

a. Changes in the release controlling excipient(s), expressed as percentage (w/w) of total release controlling excipient(s) in the formulation less than or equal to 5% w/w of total release controlling excipient content in the modified release solid oral dosage form.

The drug substance in the product is formulated to 100% of label/potency. The total additive effect of all release controlling excipient changes should not be more than 5% w/w of the total release controlling excipients in the original approved formulation.[4] The total weight of the dosage form should still be within the approved original application range.

The components (active and excipients) in the formulation should have numerical targets that represent the nominal composition of the product on which any future changes in the composition of the product are to be based. Allowable changes in the composition should be based on the original approved target composition and not on previous level 1 changes in the composition. For products approved with only a range for excipients, the target value may be assumed to be the midpoint of the original approved application range.

[4]Example: In a product consisting of active ingredient A, ethylcellulose and a plasticizer, the ethylcellulose and plasticizer content should not vary by more than an absolute total of 5% w/w of the total release controlling excipients (e.g., ethylcellulose content increases by 2.5% and plasticizer content increases by 2.5%) relative to the original approved total release controlling excipient content weight in the modified release solid oral dosage form if it is to stay within the given range allowed for level 1.

2. Test Documentation

a. Chemistry documentation

Application/compendial product release requirements.

Stability: First production batch on long-term stability data reported in annual report.

b. Dissolution documentation

None beyond application/compendial requirements.

c. Bioequivalence documentation

None.

3. Filing Documentation

Annual report (all information including long-term stability data).

B. Level 2 Change

1. Definition of Level

Level 2 changes are those that could have a significant impact on formulation quality and performance. Test documentation for a level 2 change would vary depending on whether the product could be considered to have a narrow therapeutic range.[5]

[5]At present, there is no official CDER list of narrow therapeutic range drugs. A list was developed earlier in a preliminary attempt to identify drugs where there was greater concern that deviation from the specifications and potential changes in bioavailability could raise clinical issues. This preliminary list was not based solely on 21 CFR 320.33(c) which is contained in a section of the regulations related to criteria and evidence to assess actual or potential bioequivalence problems, nor does it accurately reflect the Agency's opinion on narrow therapeutic range drugs. Currently, the issue of narrow therapeutic range drugs is under discussion within CDER. If unsure about the classification of a drug as a narrow therapeutic range drug, sponsors should contact the appropriate CDER review division.

Examples:

a. Change in the technical grade and/or specifications of the release controlling excipient(s).[6]

b. Changes in the release controlling excipient(s), expressed as percentage (w/w) of total release controlling excipient(s) in the formulation, greater than those listed above for a level 1 change, but less than or equal to 10% w/w of total release controlling excipient content in the modified release solid oral dosage form.

The drug substance in the drug product is formulated to 100% of label/potency. The total additive effect of all release controlling excipient changes should not be more than 10% w/w of the total release controlling excipient(s) in the original approved formulation. The total weight of the dosage form could still be within or outside the approved original application range.

The components (active and excipients) in the formulation should have numerical targets that represent the nominal composition of the product on which any future changes in the composition of the product are to be based. Allowable changes in the composition are based on the original approved target composition and not on the composition based on previous level 1 or level 2 changes. For products approved with only a range for excipients, the target value may be assumed to be the midpoint of the original approved application range.

2. Test Documentation

a. Chemistry documentation

Application/compendial product release requirements and updated executed batch records.

Stability:

- Nonnarrow therapeutic range drugs: One batch with three months' accelerated stability data reported in prior approval supplement and long-term stability data of first production batch reported in annual report.

[6]Example: Eudragit RS-100 vs. Eudragit RL-100.

- Narrow therapeutic range drugs: Three batches with three months' accelerated stability data reported in prior approval supplement and long-term stability data of first three production batches reported in annual report.

b. Dissolution documentation

- Nonnarrow therapeutic range drugs

Extended release: In addition to application/compendial release requirements, multipoint dissolution profiles should be obtained in three other media, for example, in water, 0.1N HCl, and USP buffer media at pH 4.5, and 6.8 for the changed drug product and the biobatch or marketed batch (unchanged drug product). Adequate sampling should be performed, for example, at 1, 2, and 4 hours and every two hours thereafter until either 80% of the drug from the drug product is released or an asymptote is reached. A surfactant may be used with appropriate justification.

Delayed release: In addition to application/compendial release requirements, dissolution tests should be performed in 0.1 N HCl for 2 hours (acid stage) followed by testing in USP buffer media in the range of pH 4.5-7.5 (buffer stage) under standard (application/compendial) test conditions and two additional agitation speeds using the application/compendial test apparatus (three additional test conditions). If the application/compendial test apparatus is the rotating basket method (Apparatus 1), a rotation speed of 50, 100, and 150 rpm may be used, and if the application/compendial test apparatus is the rotating paddle method (Apparatus 2), a rotation speed of 50, 75, and 100 rpm may be used. Multipoint dissolution profiles should be obtained during the buffer stage of testing. Adequate sampling should be performed, for example, at 15, 30, 45, 60, and 120 minutes (following the time from which the dosage form is placed in the buffer) until either 80% of the drug from the drug product is released or an asymptote is reached. The above dissolution testing should be performed using the changed drug product and the biobatch or marketed batch (unchanged drug product).

All modified release solid oral dosage forms: In the presence of an established in vitro/in vivo correlation (6), only application/compendial dissolution testing should be performed (i.e., only in vitro release data by the correlating method should be submitted). The dissolution profiles of the changed drug product and the biobatch or marketed batch (unchanged drug product) should be similar. The sponsor should apply appropriate statistical testing with justifications (e.g., the f_2 equation) for comparing

dissolution profiles (5). Similarity testing for the two dissolution profiles (i.e., for the unchanged drug product and the changed drug product) obtained in each individual medium is appropriate.

- Narrow therapeutic range drugs

Extended release: In addition to application/compendial release requirements, a multipoint dissolution profile should be obtained in application/compendial medium for the changed drug product and the biobatch or marketed batch (unchanged drug product). Adequate sampling should be performed, for example at 1, 2, and 4 hours and every two hours thereafter until either 80% of the drug from the drug product is released or an asymptote is reached.

Delayed release: In addition to application/compendial release requirements, a multipoint dissolution profile should be obtained during the buffer stage of testing using the application/compendial medium for the changed drug product and the biobatch or marketed batch (unchanged drug product). Adequate sampling should be performed, for example, at 15, 30, 45, 60, and 120 minutes (following the time from which the dosage form is placed in the buffer) until either 80% of the drug from the drug product is released or an asymptote is reached.

c. Bioequivalence documentation

- Nonnarrow therapeutic range drugs: None.

- Narrow therapeutic range drugs: A single-dose bioequivalence study (3). The bioequivalence study may be waived in the presence of an established in vitro/in vivo correlation (6). Changes in release controlling excipients in the formulation should be within the range of release controlling excipients of the established correlation.

3. Filing Documentation

Prior approval supplement (all information including accelerated stability data); annual report (long-term stability data).

C. Level 3 Change

1. Definition of Level

Level 3 changes are those that are likely to have a significant impact on formulation quality and performance affecting all therapeutic ranges of the drug. Examples:

a. Addition or deletion of release controlling excipient(s) (e.g., release controlling polymer/plasticizer).

b. Changes in the release controlling excipient(s), expressed as percentage (w/w) of total release controlling excipient(s) in the formulation, greater than those listed above for a level 2 change (i.e., greater than 10% w/w of total release controlling excipient content in the modified release solid oral dosage form). Total weight of the dosage form may be within or outside the original approved application range.

2. Test Documentation

a. Chemistry documentation

Application/compendial product release requirements and updated executed batch records.

Stability: Three batches with three months' accelerated stability data reported in prior approval supplement and long-term stability data of first three production batches reported in annual report.

b. Dissolution documentation

Extended release: In addition to application/compendial release requirements, a multipoint dissolution profile should be obtained using application/compendial test conditions for the changed drug product and the biobatch or marketed batch (unchanged drug product). Adequate sampling should be performed, for example at 1, 2, and 4 hours and every two hours thereafter until either 80% of the drug from the drug product is released or an asymptote is reached.

Delayed release: In addition to application/compendial release requirements, a multipoint dissolution profile should be obtained during the buffer stage of testing using the application/compendial test conditions for

the changed drug product and the biobatch or marketed batch (unchanged drug product). Adequate sampling should be performed, for example at 15, 30, 45, 60, and 120 minutes (following the time from which the dosage form is placed in the buffer) until either 80% of the drug from the drug product is released or an asymptote is reached.

c. Bioequivalence documentation

A single-dose bioequivalence study (3). The bioequivalence study may be waived in the presence of an established in vitro/in vivo correlation (6). Changes in release controlling excipients in the formulation should be within the range of release controlling excipients of the established correlation.

3. Filing Documentation

Prior approval supplement (all information including accelerated stability data); annual report (long-term stability data).

V. SITE CHANGES

Site changes consist of changes in location of the site of manufacture, packaging operations, and/or analytical testing laboratory for both company-owned and contract manufacturing facilities. They do not include any scale-up changes, changes in manufacturing (including process and/or equipment), or changes in components or composition. New manufacturing locations should have had a satisfactory current good manufacturing practice (cGMP) inspection.

A stand-alone packaging operations site change, using container(s)/closure(s) in the approved application, may be submitted as a Changes Being Effected supplement. The facility should also have a current and satisfactory cGMP compliance profile with the FDA for the type of packaging operation in question before submitting the supplement. If the facility has not received a satisfactory cGMP inspection for the type of packaging operation in question, a prior approval supplement is recommended. The supplement should contain a written certification from the packaging facility stating that it is in conformance with cGMPs. It should also contain a commitment to place the first production batch of the product, and annual batches thereafter, on long-term stability studies using the approved protocol in the application and to submit the resulting data in annual reports. Where the product is available in more than one strength, size, or container/closure system, one lot of each combination should be placed on long-term stability studies. Bracketing or matrixing is allowed only if it has been approved previously by the FDA. Any changes to an approved stability protocol should have a supplemental approval prior to the initiation of the stability study.

A stand-alone analytical testing laboratory site change may be submitted as a Changes Being Effected supplement if the new facility has a current and satisfactory cGMP compliance profile with the FDA for the type of testing operation in question. The supplement should contain a commitment to use the same test methods employed in the approved application, written certification from the testing laboratory stating that they are in conformance with cGMPs, and a full description of the testing to be performed by the testing lab. If the facility has not received a satisfactory cGMP inspection for the type of testing involved, a prior approval supplement is recommended.

A. Level 1 Change

1. Definition of Level

Level 1 changes consist of site changes within a single facility where the same equipment, standard operating procedures (SOPs), environmental conditions (e.g., temperature and humidity) and controls, and personnel common[7] to both manufacturing sites are used and where no changes are made to the executed batch records, except for administrative information and the location of the facility.

2. Test Documentation

a. Chemistry documentation

None beyond application/compendial product release requirements.

b. Dissolution documentation

None beyond application/compendial release requirements.

c. Bioequivalence documentation

None.

3. Filing Documentation

Annual report.

[7] *Common* is defined as employees already working on the campus who have suitable experience with the manufacturing process.

B. Level 2 Change

1. Definition of Level

Level 2 changes consist of site changes within a contiguous campus, or between facilities in adjacent city blocks, where the same equipment, SOPs, environmental conditions (e.g., temperature and humidity) and controls, and personnel common to both manufacturing sites are used and where no changes are made to the executed batch records, except for administrative information and the location of the facility.

2. Test Documentation

a. Chemistry documentation

Notification of location of new site and updated executed batch records. None beyond application/compendial product release requirements.

Stability: One batch with three months accelerated stability data reported in Changes Being Effected supplement and long-term stability data of first production batch reported in annual report.

b. Dissolution documentation

Extended release: In addition to application/compendial release requirements, multipoint dissolution profiles should be obtained in three other media, for example, in water, 0.1N HCl, and USP buffer media at pH 4.5, and 6.8 for the changed drug product and the biobatch or marketed batch (unchanged drug product). Adequate sampling should be performed, for example at 1, 2, and 4 hours and every two hours thereafter until either 80% of the drug from the drug product is released or an asymptote is reached. A surfactant may be used with appropriate justification.

Delayed release: In addition to application/compendial release requirements, dissolution tests should be performed in 0.1 N HCl for 2 hours (acid stage) followed by testing in USP buffer media, in the range of pH 4.5-7.5 (buffer stage) under standard (application/compendial) test conditions and two additional agitation speeds using the application/ compendial test apparatus (three additional test conditions). If the application/compendial test apparatus is the rotating basket method (Apparatus 1), a rotation speed of 50, 100, and 150 rpm may be used, and if the application/compendial test apparatus is the rotating paddle method (Apparatus 2), a rotation speed of 50, 75, and 100 rpm may be used.

Multipoint dissolution profiles should be obtained during the buffer stage of testing. Adequate sampling should be performed, for example, at 15, 30, 45, 60, and 120 minutes (following the time from which the dosage form is placed in the buffer) until either 80% of the drug from the drug product is released or an asymptote is reached. The above dissolution testing should be performed using the changed drug product and the biobatch or marketed batch (unchanged drug product).

All modified release solid oral dosage forms: In the presence of an established in vitro/in vivo correlation (6), only application/compendial dissolution testing should be performed (i.e., only in vitro release data by the correlating method should be submitted). The dissolution profiles of the changed drug product and the biobatch or marketed batch (unchanged drug product) should be similar. The sponsor should apply appropriate statistical testing with justifications (e.g., the f_2 equation) for comparing dissolution profiles (5). Similarity testing for the two dissolution profiles (i.e., for the unchanged drug product and the changed drug product) obtained in each individual medium is appropriate.

c. Bioequivalence documentation

None.

3. Filing Documentation

Changes Being Effected supplement (all information including accelerated stability data); annual report (long-term stability data).

C. Level 3 Change

1. Definition of Level

Level 3 changes consist of a change in manufacturing site to a different campus. A different campus is defined as one that is not on the same original contiguous site or where the facilities are not in adjacent city blocks. To qualify as a level 3 change, the same equipment, SOPs, environmental conditions, and controls should be used in the manufacturing process at the new site, and no changes may be made to the executed batch records except for administrative information, location and language translation, where needed.

2. Test Documentation

a. Chemistry documentation

Notification of location of new site and updated executed batch records. Application/compendial product release requirements.

Stability:

Significant body of information available: One batch with three months' accelerated stability data reported in prior approval supplement and long-term stability data of first three production batches reported in annual report.

Significant body of information not available: Three batches with three months' accelerated stability data reported in prior approval supplement and long-term stability data of first three production batches reported in annual report.

b. Dissolution documentation

Extended release: In addition to application/compendial release requirements, a multipoint dissolution profile should be obtained using application/compendial test conditions for the changed drug product and the biobatch or marketed batch (unchanged drug product). Adequate sampling should be performed, for example at 1, 2, and 4 hours and every two hours thereafter until either 80% of the drug from the drug product is released or an asymptote is reached.

Delayed release: In addition to application/compendial release requirements, a multipoint dissolution profile should be obtained during the buffer stage of testing using the application/compendial test conditions for the changed drug product and the biobatch or marketed batch (unchanged drug product). Adequate sampling should be performed, for example, at 15, 30, 45, 60, and 120 minutes (following the time from which the dosage form is placed in the buffer) until either 80% of the drug from the drug product is released or an asymptote is reached.

c. Bioequivalence documentation

A single-dose bioequivalence study (3). The bioequivalence study may be waived in the presence of an established in vitro/in vivo correlation (6).

3. Filing Documentation

Prior approval supplement (all information including accelerated stability test data); annual report (long-term stability data).

VI. CHANGES IN BATCH SIZE (SCALE-UP/SCALE-DOWN)

Postapproval changes in the size of a batch from the pivotal/pilot scale biobatch material to larger or smaller production batches call for submission of additional information to the application. Scale-down below 100,000 dosage units is not covered by this guidance. Adjustments in parameters such as mixing times and speeds may be made to tailor the process to the characteristics of larger or smaller scale equipment. All scale-up changes should be properly validated and, where needed, inspected by appropriate Agency personnel.

A. Level 1 Change

1. Definition of Level

Change in batch size, up to and including a factor of ten times the size of the pilot/biobatch, where (1) the equipment used to produce the test batch(es) may vary in capacity, but are of the same design and operating principles; (2) the batch(es) is manufactured in full compliance with cGMPs; and (3) the same standard operating procedures (SOPs) and controls, as well as the same formulation and manufacturing procedures, are used on the test batch(es) and on the full-scale production batch(es).

2. Test Documentation

a. Chemistry documentation

Application/compendial product release requirements. Notification of change and submission of updated executed batch records in annual report.

Stability: First production batch on long-term stability data reported in annual report.

b. Dissolution documentation

None beyond application/compendial release requirements.

c. Bioequivalence documentation

None.

3. Filing Documentation

Annual report (all information including long-term stability data).

B. Level 2 Change

1. Definition of Level

Changes in batch size beyond a factor of ten times the size of the pilot/biobatch where (1) the equipment used to produce the test batch(es) is of the same design and operating principles; (2) the batch(es) is manufactured in full compliance with cGMPs; and (3) the same SOPs and controls as well as the same formulation and manufacturing procedures are used on the test batch(es) and on the full-scale production batch(es).

2. Test Documentation

a. Chemistry documentation

Application/compendial product release requirements.

Notification of change and submission of updated batch records.

Stability: One batch with three months' accelerated stability data reported in Changes Being Effected supplement and long-term stability data of first production batch reported in annual report.

b. Dissolution documentation

Extended release: In addition to application/compendial release requirements, multipoint dissolution profiles should be obtained in three other media, for example, in water, 0.1N HCl, and USP buffer media at pH 4.5, and 6.8 for the changed drug product and the biobatch or marketed batch (unchanged drug product). Adequate sampling should be performed, for example, at 1, 2, and 4 hours, and every two hours thereafter until either 80% of the drug from the drug product is released or an asymptote is reached. A surfactant may be used with appropriate justification.

Delayed release: In addition to application/compendial release requirements, dissolution tests should be performed in 0.1 N HCl for 2

hours (acid stage) followed by testing in USP buffer media in the range of pH 4.5-7.5 (buffer stage) under standard (application/compendial) test conditions and two additional agitation speeds using the application/ compendial test apparatus (three additional test conditions). If the application/compendial test apparatus is the rotating basket method (Apparatus 1), a rotation speed of 50, 100, and 150 rpm may be used, and if the application/compendial test apparatus is the rotating paddle method (Apparatus 2), a rotation speed of 50, 75, and 100 rpm may be used. Multipoint dissolution profiles should be obtained during the buffer stage of testing. Adequate sampling should be performed, for example, at 15, 30, 45, 60, and 120 minutes (following the time from which the dosage form is placed in the buffer) until either 80% of the drug from the drug product is released or an asymptote is reached. The above dissolution testing should be performed using the changed drug product and the biobatch or marketed batch (unchanged drug product).

All modified release solid oral dosage forms: In the presence of an established in vitro/in vivo correlation (6), only application/compendial dissolution testing should be performed (i.e., only in vitro release data by the correlating method should be submitted). The dissolution profiles of the changed drug product and the biobatch or marketed batch (unchanged drug product) should be similar. The sponsor should apply appropriate statistical testing with justifications (e.g., the f_2 equation) for comparing dissolution profiles (5). Similarity testing for the two dissolution profiles (i.e., for the unchanged drug product and the changed drug product) obtained in each individual medium is appropriate.

c. Bioequivalence documentation

None.

3. Filing Documentation

Changes Being Effected supplement (all information including accelerated stability data); annual report (long-term stability data).

VII. MANUFACTURING EQUIPMENT CHANGES

Manufacturing changes may involve the equipment used in the manufacturing process (critical manufacturing variable). If a manufacturer wishes to use manufacturing equipment that is not identical in every respect to the original manufacturing equipment used in the approved application, appropriate validation studies should be conducted to demonstrate that the new

equipment is similar to the original equipment. For modified release solid oral dosage forms, consideration should be given as to whether or not the change in manufacturing equipment is critical to drug release (critical equipment variable).

A. Level 1 Change

1. Definition of Level

This category consists of (1) change from nonautomated or nonmechanical equipment to automated or mechanical equipment to move ingredients and (2) change to alternative equipment of the same design and operating principles of the same or of a different capacity.

2. Test documentation

a. Chemistry documentation

Application/compendial product release requirements. Notification of change and submission of updated executed batch records.

Stability: First production batch on long-term stability data reported in annual report.

b. Dissolution documentation

None beyond application/compendial release requirements.

c. Bioequivalence documentation

None.

3. Filing Documentation

Annual report (all information including long-term stability data).

B. Level 2 Change

1. Definition of Level

Change in equipment to a different design and different operating principles.

2. Test Documentation

a. Chemistry documentation

Application/compendial product release requirements. Notification of change and submission of updated executed batch records.

Stability:

Significant body of information available: One batch with three months' accelerated stability data reported in prior approval supplement and long-term stability data of first three production batches reported in annual report.

Significant body of information not available: Three batches with three months' accelerated stability data reported in prior approval supplement and long-term stability data of first three production batches reported in annual report.

b. Dissolution documentation

Extended release: In addition to application/compendial release requirements, multipoint dissolution profiles should be obtained in three other media, for example, in water, 0.1N HCl, and USP buffer media at pH 4.5, and 6.8 for the changed drug product and the biobatch or marketed batch (unchanged drug product). Adequate sampling should be performed, for example, at 1, 2, and 4 hours and every two hours thereafter until either 80% of the drug from the drug product is released or an asymptote is reached. A surfactant may be used with appropriate justification.

Delayed release: In addition to application/compendial release requirements, dissolution tests should be performed in 0.1 N HCl for 2 hours (acid stage) followed by testing in USP buffer media, in the range of pH 4.5-7.5 (buffer stage) under standard (application/compendial) test conditions and two additional agitation speeds using the application/ compendial test apparatus (three additional test conditions). If the application/compendial test apparatus is the rotating basket method (Apparatus 1), a rotation speed of 50, 100, and 150 rpm may be used, and if the application/compendial test apparatus is the rotating paddle method (Apparatus 2), a rotation speed of 50, 75, and 100 rpm may be used. Multipoint dissolution profiles should be obtained during the buffer stage of testing. Adequate sampling should be performed, for example, at 15, 30, 45, 60, and 120 minutes (following the time from which the dosage form is placed in the buffer) until either 80% of the drug from the drug product is released or an asymptote is reached. The above dissolution

testing should be performed using the changed drug product and the biobatch or marketed batch (unchanged drug product).

All modified release solid oral dosage forms: In the presence of an established in vitro/in vivo correlation (6), only application/compendial dissolution testing should be performed (i.e., only in vitro release data by the correlating method should be submitted). The dissolution profiles of the changed drug product and the biobatch or marketed batch (unchanged drug product) should be similar. The sponsor should apply appropriate statistical testing with justifications (e.g., the f_2 equation) for comparing dissolution profiles (5). Similarity testing for the two dissolution profiles (i.e., for the unchanged drug product and the changed drug product) obtained in each individual medium is appropriate.

c. Bioequivalence documentation

None.

3. Filing Documentation

Prior approval supplement with justification for change (all information including accelerated stability data); annual report (long-term stability data).

VIII. MANUFACTURING PROCESS CHANGES

Manufacturing changes may involve the manufacturing process itself (critical manufacturing variable). If a manufacturer wishes to use a manufacturing process that is not identical in every respect to the original manufacturing process used in the approved application, appropriate validation studies should be conducted to demonstrate that the new process is similar to the original process. For modified release solid oral dosage forms, consideration should be given as to whether or not the change in manufacturing process is critical to drug release (critical processing variable). For purposes of categorizing the level of changes, process change may be considered only to affect a release controlling excipient when both types of excipients (i.e., nonrelease and release controlling) are present during the unit operation undergoing a change.

A. Level 1 Change

1. Definition of Level

Process changes involving adjustment of equipment operating conditions such as mixing times and operating speeds within original approved application ranges affecting the nonrelease controlling and/or release controlling excipient(s). The

sponsor should provide appropriate justifications for claiming any excipient(s) as a nonrelease controlling or a release controlling excipient in the formulation of the modified release solid oral dosage form.

2. Test Documentation

a. Chemistry documentation

None beyond application/compendial product release requirements. Notification of the change and submission of the updated executed batch records.

b. Dissolution documentation

None beyond application/compendial release requirements.

c. Bioequivalence documentation

None.

3. Filing Documentation

Annual report.

B. Level 2 Change

1. Definition of Level

This category includes process changes involving adjustment of equipment operating conditions such as mixing times and operating speeds outside of original approved application ranges.

2. Test Documentation

a. Chemistry documentation

Application/compendial product release requirements. Notification of change and submission of updated executed batch records.

Stability: One batch with three months' accelerated stability data reported in Changes Being Effected supplement and long-term stability data of first production batch reported in annual report.

b. Dissolution documentation

Extended release: In addition to application/compendial release requirements, multipoint dissolution profiles should be obtained in three other media, for example, in water, 0.1N HCl, and USP buffer media at pH 4.5, and 6.8 for the changed drug product and the biobatch or marketed batch (unchanged drug product). Adequate sampling should be performed, for example at 1, 2, and 4 hours and every two hours thereafter until either 80% of the drug from the drug product is released or an asymptote is reached. A surfactant may be used with appropriate justification.

Delayed release: In addition to application/compendial release requirements, dissolution tests should be performed in 0.1 N HCl for 2 hours (acid stage) followed by testing in USP buffer media, in the range of pH 4.5-7.5 (buffer stage) under standard (application/compendial) test conditions and two additional agitation speeds using the application/ compendial test apparatus (three additional test conditions). If the application/compendial test apparatus is the rotating basket method (Apparatus 1), a rotation speed of 50, 100, and 150 rpm may be used, and if the application/compendial test apparatus is the rotating paddle method (Apparatus 2), a rotation speed of 50, 75, and 100 rpm may be used. Multipoint dissolution profiles should be obtained during the buffer stage of testing. Adequate sampling should be performed, for example, at 15, 30, 45, 60, and 120 minutes (following the time from which the dosage form is placed in the buffer) until either 80% of the drug from the drug product is released or an asymptote is reached. The above dissolution testing should be performed using the changed drug product and the biobatch or marketed batch (unchanged drug product).

All modified release solid oral dosage forms: In the presence of an established in vitro/in vivo correlation (6), only application/compendial dissolution testing should be performed (i.e., only in vitro release data by the correlating method should be submitted). The dissolution profiles of the changed drug product and the biobatch or marketed batch (unchanged drug product) should be similar. The sponsor should apply appropriate statistical testing with justifications (e.g., the f_2 equation) for comparing dissolution profiles (5). Similarity testing for the two dissolution profiles (i.e., for the unchanged drug product and the changed drug product) obtained in each individual medium is appropriate.

c. Bioequivalence documentation

None.

3. Filing Documentation

Changes Being Effected supplement (all information including accelerated stability data); annual report (long-term stability data).

C. Level 3 Change

1. Definition of Level

This category includes change in the type of process used in the manufacture of the product, such as a change from wet granulation to direct compression of dry powder.

2. Test Documentation

a. Chemistry documentation

Application/compendial product release requirements. Notification of change and submission of updated executed batch records.

Stability: Three batches with three months' accelerated stability data reported in prior approval supplement and long-term stability data of first three production batches reported in annual report.

b. Dissolution documentation

Extended release: In addition to application/compendial release requirements, a multipoint dissolution profile should be obtained using application/compendial test conditions for the changed drug product and the biobatch or marketed batch (unchanged drug product). Adequate sampling should be performed, for example at 1, 2, and 4 hours and every two hours thereafter until either 80% of the drug from the drug product is released or an asymptote is reached.

Delayed release: In addition to application/compendial release requirements, a multipoint dissolution profile should be obtained during the buffer stage of testing using the application/compendial test conditions for the changed drug product and the biobatch or marketed batch (unchanged drug product). Adequate sampling should be performed, for example at

15, 30, 45, 60, and 120 minutes (following the time from which the dosage form is placed in the buffer) until either 80% of the drug from the drug product is released or an asymptote is reached.

c. Bioequivalence documentation

A single-dose bioequivalence study (3). The bioequivalence study may be waived in the presence of an established in vitro/in vivo correlation (6).

3. Filing Documentation

Prior approval supplement (all information including accelerated stability data); annual report (long-term stability data).

GLOSSARY OF TERMS

The following terms and their definitions (9) are being provided to assist the reader in using this guidance document.

Batch: A specific quantity of a drug or other material produced according to a single manufacturing order during the same cycle of manufacture and intended to have uniform character and quality, within specified limits (21 CFR 210.3(b)(2)).

Batch formula (Composition): A complete list of the ingredients and their amounts to be used for the manufacture of a representative batch of the drug product. All ingredients should be included in the batch formula whether or not they remain in the finished product (1).

Biobatch: The lot of drug product formulated for purposes of pharmacokinetic evaluation in a bioavailability/bioequivalency study. For modified release solid oral, this batch should be 10% or greater than the proposed commercial production batch or at least 100,000 units, whichever is greater.

Bioequivalence Studies For Modified Release Drug Product: Refer to the OGD Guidance (3). The bioequivalence study should be conducted using the reference listed drug (RLD) product and/or the innovator drug product as the reference and the test product should be the product (generic or innovator) which has undergone postapproval change.

Contiguous Campus: Continuous or unbroken site or a set of buildings in adjacent city blocks.

Critical Equipment Variable: A specific design, operating principle, or automation of equipment that can affect a specific performance variable critical to the ultimate and predictable performance of the dosage form and its drug.

Critical Manufacturing Variable: Includes those manufacturing materials (critical composition variable), methods, equipment, and processes that significantly affect drug release, from the formulation (e.g., coating thickness, particle size, crystal form, excipient type, concentrations and distribution, and tablet hardness).

Critical Processing Variable: A specific step, unit process, or condition of a unit process that can affect a specific performance variable critical to the ultimate and predictable performance of the dosage form and its drug.

Delayed Release: Release of a drug (or drugs) at a time other than immediately following oral administration.

Dissolution Testing: Extended release: Dissolution testing should be conducted on 12 individual dosage units for the changed drug product and the biobatch or marketed batch

(unchanged drug product). The potential for pH dependence of drug release from a modified release drug product is well recognized. Multipoint dissolution profiles should be obtained using discriminating agitation speed and medium. A surfactant may be used with appropriate justification. Early sampling times of 1, 2, and 4 hours should be included in the sampling schedule to provide assurance against premature release of the drug (dose dumping) from the formulation. Differing sampling times should be justified to prevent premature drug release. See current USP 23 NF 18, sections <711> and <724>, for general dissolution requirements. The general dissolution conditions to be followed are shown below:

1. Apparatus: USP 23 Apparatus 1 (rotating basket)
   USP 23 Apparatus 2 (rotating paddle)
   USP 23 Apparatus 3 (reciprocating cylinder)*
   USP 23 Apparatus 4 (flow-through cell)*
   USP 23 Apparatus 7 (reciprocating disk)*

2. Rotation Speed: 50, 100, and 150 rpm (basket)
   50, 75 and 100 rpm (paddle)

3. Temperature: 37±0.5°C

4. Units To Be Tested: 12

5. Dissolution Volume: 500-1000 mL

6. Dissolution Medium: Aqueous media of various pH.

7. Sampling Schedule: Adequate sampling should be performed, for example at 1, 2, and 4 hours, and every two hours thereafter until either 80% of the drug is released or an asymptote is reached.

8. Tolerances: As established.

9. Content Uniformity: Content uniformity testing of the proposed product lot should be performed as described in USP 23.

   *When using USP 23 Apparatus 3 (reciprocating cylinder), USP 23 Apparatus 4 (flow-through cell), or USP 23 Apparatus 7 (reciprocating disk) the above dissolution testing conditions should be modified accordingly.

Delayed release: For enteric coated drug products, drug release procedures described in USP 23 NF 18, sections <711> and <724> should be followed. When the guidance refers to dissolution testing in addition to application/compendial release requirements, the dissolution test should be performed in 0.1N HCl for 2 hours (acid stage) followed by testing in USP buffer media, in the range of pH 4.5-7.5 (buffer stage) under standard (application/compendial) test conditions and

increased agitation speeds using the application/ compendial test apparatus. For the rotating basket method (Apparatus 1), a rotation speed of 50, 100, and 150 rpm may be used and for the rotating paddle method (Apparatus 2), a rotation speed of 50, 75, and 100 rpm may be studied. Multipoint dissolution profiles should be obtained during the buffer stage of testing. Adequate sampling should be performed, for example, at 15, 30, 45, 60, and 120 minutes (following the time from which the dosage form is placed in the buffer) until either 80% of the drug is released or an asymptote is reached. The above dissolution testing should be performed using the changed drug product and the biobatch or marketed batch (unchanged drug product).

Drug Product: A drug product is a finished dosage form (e.g., tablet and capsule) that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients (21 CFR 314.3(b)). A solid oral dosage form includes but is not limited to tablets, chewable tablets, enteric coated tablets, capsules, caplets, encapsulated beads, and gelcaps.

Drug Substance: An active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of a disease, or to affect the structure of any function of the human body, but does not include intermediates used in the synthesis of such ingredient (21 CFR 314.3(b)).

Enteric Coated: Intended to delay the release of the drug (or drugs) until the dosage form has passed through the stomach. Enteric coated products are delayed release dosage forms.

Equipment: Automated or nonautomated, mechanical or nonmechanical equipment used to produce the drug product, including equipment used to package the drug product.

Extended Release: Extended release products are formulated to make the drug available over an extended period after ingestion. This allows a reduction in dosing frequency compared to a drug presented as a conventional dosage form (e.g., as a solution or an immediate release dosage form).

Formulation: A listing of the ingredients and composition of the dosage form.

Immediate Release: Allows the drug to dissolve in the gastrointestinal contents, with no intention of delaying or prolonging the dissolution or absorption of the drug.

In Vitro Dissolution Profile Comparison: Model Independent Approach Using Similarity Factor: Dissolution profiles may be compared using the following equation that defines a similarity factor (f_2):

$$f_2 = 50 \text{ LOG } \{[1+1/n \sum_{t=1}^{n} (R_t-T_t)^2]^{-0.5} \text{ x } 100\}$$

where LOG = logarithm to base 10, n = number of sampling time points, $\sum$ = summation over all time points, R_t = dissolution at time point t of the reference (unchanged drug product, i.e., pre-

change batch), T_t = dissolution at time point t of the test (changed drug product, i.e., post-change batch) (5 and 8).

For comparison of multipoint dissolution profiles obtained in multiple media, similarity testing should be performed using pairwise dissolution profiles (i.e., for the unchanged and changed product) obtained in each individual medium. It is recommended that only one point past the plateau of the profiles be used in calculating the f_2 value. A correction for a lag time prior to similarity testing should not be performed unless justified.

An f_2 value between 50 and 100 suggests the two dissolution profiles are similar. Also, the average difference at any dissolution sampling time point should not be greater than 15% between the changed drug product and the biobatch or marketed batch (unchanged drug product) dissolution profiles. An appropriate reference for this comparison should represent an average dissolution profile derived from at least three consecutive recent batches of the unchanged drug product (biobatch or marketed batch). Finally, the dissolution data obtained under the application/compendial dissolution testing conditions (media, agitation, etc.), on both the changed drug product and the biobatch or marketed batch (unchanged drug product) should be within the application/compendial specifications.

An f_2 value less than 50 does not necessarily indicate lack of similarity. If the sponsor is of the opinion that the differences observed related to this calculation of f_2 are typical for the drug product involved in this SUPAC situation, an appropriate justification can be submitted, but only as part of a prior approval supplement. This justification should include additional data to support the claim of similarity, as well as supporting statistical analysis (e.g. 90% confidence interval analysis). If this justification is not found acceptable, the potential effect of the proposed change on the differences in dissolution on bioavailability should be determined.

Dissolution profiles can also be compared using other model independent or model dependent methods (5).

In Vitro-In Vivo Correlation: A predictive mathematical model describing the relationship between an in vitro property of an oral dosage form (usually the rate or extent of drug dissolution or release) and a relevant in vivo response (e.g., plasma drug concentration or amount of drug absorbed).

For modified release dosage forms, changes in release controlling excipients in the formulation should be within the range of release controlling excipients of the established correlation. In the presence of an established in vitro/in vivo correlation (6), only application/ compendial dissolution testing need be performed. Also, an established in vitro/in vivo correlation can be used for any level of changes described in this guidance.

Justification: Reports containing scientific data and expert professional judgment to substantiate decisions.

Lot: A batch or a specific identified portion of a batch, having uniform character and quality within specified limits or, in the case of a drug product produced by continuous process, a specific identified amount produced in a unit of time or quantity in a manner that assures its having uniform character and quality within specified limits (21 CFR 210.3(b)(10)).

Modified Release Dosage Forms: Dosage forms whose drug-release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as a solution or an immediate release dosage form. Modified release solid oral dosage forms include both delayed and extended release drug products.

Nonrelease Controlling Excipient (Non-Critical Composition Variable): An excipient in the final dosage form whose primary function does not include modifying the duration of release of the active drug substance from the dosage form.

Operating Principles: Rules or concepts governing the operation of the system.

Pilot Scale: The manufacture of either drug substance or drug product by a procedure fully representative of and simulating that used for full manufacturing scale. For solid oral dosage forms this is generally taken to be, at a minimum, one tenth that of full production, or 100,000 tablets or capsules, whichever is larger (4).

Process: A series of operations, actions and controls used to manufacture a drug product.

Ranges: The extent to which or the limits between which acceptable variation exists.

Release Controlling Excipient (Critical Composition Variable): An excipient in the final dosage form whose primary function is to modify the duration of release of the active drug substance from the dosage form.

Release Mechanism: The process by which the drug substance is released from the dosage form. Typically the definition contains the energy source or pictorially describes the way the drug is released.

Representative: Corresponding to or replacing some other species or the like; exemplifying a group or kind; typical.

Same: Agreeing in kind, amount; unchanged in character or condition.

Satisfactory Current Good Manufacturing Practice (cGMP) Inspection: A satisfactory cGMP inspection is one during which (1) no objectionable conditions or practices were found during an inspection or (2) objectionable conditions were found, however, corrective action is left to the firm to take voluntarily and the objectionable conditions do not justify further administrative or regulatory actions.

Scale-up: The process of increasing the batch size.

Scale-down: The process of decreasing the batch size.

Significant Body of Information:

- Immediate Release Solid Oral Dosage Forms: A significant body of information on the stability of the drug product is likely to exist after five years of commercial experience for new molecular entities, or three years of commercial experience for new dosage forms.

- Modified Release Solid Oral Dosage Forms: A significant body of information should include, for "Modified Release Solid Oral Dosage Forms," a product-specific body of information. This product-specific body of information is likely to exist after five years of commercial experience for the original modified release solid oral drug product, or three years of commercial experience for any subsequent modified release solid oral drug product utilizing similar drug release mechanism.

Similar: Having a general likeness.

Technical Grade: Technical grades of excipients may differ in (1) specifications and/or functionality, (2) impurities, and (3) impurity profiles.

Validation: Establishing through documented evidence a high degree of assurance that a specific process will consistently produce a product that meets its predetermined specifications and quality attributes. A validated manufacturing process is one that has been proven to do what it purports or is represented to do. The proof of validation is obtained through collection and evaluation of data, preferably beginning from the process development phase and continuing through into the production phase. Validation necessarily includes process qualification (the qualification of materials, equipment, systems, buildings, and personnel), but it also includes the control of entire processes for repeated batches or runs.

REFERENCES

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   Office of Generic Drugs, CDER, September 13, 1990.

3. FDA, *Oral Extended (Controlled) Release Dosage Forms In Vivo Bioequivalence and In Vitro Dissolution Testing,* September 1993.

4. FDA, *Stability Testing of New Drug Substances and Products; ICH Guideline, Federal Register,* Vol. 59, No. 183, 48754-48759, September 1994.

5. FDA, *Guidance for Dissolution Testing of Immediate Release Solid Oral Products, 1997.*

6. FDA, *Guidance for the Development, Evaluation and Application of In Vitro/In Vivo Correlations for Extended Release Solid Oral Dosage Forms, 1997.*

7. FDA/University of Maryland Manufacturing Research Contract Summary.

8. Moore, J. W. and H. H. Flanner, "Mathematical Comparison of Dissolution Profiles," *Pharmaceutical Technology*, 6:64-74, 1996.

9. Skelly, J. P., et al., "Workshop Report: Scaleup of Oral Extended-Release Dosage Forms," *Pharmaceutical Research*, 10(12): 1800-1805, 1993.

EXTENDED RELEASE SOLID ORAL DOSAGE FORMS
NON-RELEASE CONTROLLING COMPONENTS AND COMPOSITION

LEVEL	CLASSIFICATION	THERAPEUTIC RANGE	TEST DOCUMENTATION	FILING DOCUMENTATION
I	-COMPLETE OR PARTIAL DELETION OF COLOR/FLAVOR -CHANGE IN INKS, IMPRINTS -UPTO SUPAC-IR LEVEL 1 EXCIPIENT RANGES -NO OTHER CHANGES	ALL DRUGS	-STABILITY -APPLICATION/COMPENDIAL REQUIREMENTS -NO BIOSTUDY	-ANNUAL REPORT
II	-CHANGE IN TECHNICAL GRADE AND/OR SPECIFICATIONS -HIGHER THAN SUPAC-IR LEVEL 1 BUT LESS THAN LEVEL 2 EXCIPIENT RANGES -NO OTHER CHANGES	ALL DRUGS	-NOTIFICATION & UPDATED BATCH RECORD -STABILITY -APPLICATION/COMPENDIAL REQUIREMENTS PLUS MULTI-POINT DISSOLUTION PROFILES IN THREE OTHER MEDIA (e.g., WATER, 0.1N HCL, AND USP BUFFER MEDIA AT pH 4.5 AND 6.8) UNTIL $\geq$ 80% OF DRUG RELEASED OR AN ASYMPTOTE IS REACHED[1] -APPLY SOME STATISTICAL TEST (F2 TEST) FOR COMPARING DISSOLUTION PROFILES[2] -NO BIOSTUDY	-PRIOR APPROVAL SUPPLEMENT
III	-HIGHER THAN SUPAC-IR LEVEL 2 EXCIPIENT RANGES	ALL DRUGS	-UPDATED BATCH RECORD -STABILITY -APPLICATION/COMPENDIAL (PROFILE) REQUIREMENTS -BIOSTUDY OR IVIVC[1]	-PRIOR APPROVAL SUPPLEMENT

[1] IN THE PRESENCE OF AN ESTABLISHED IN VITRO/IN VIVO CORRELATION ONLY APPLICATION/COMPENDIAL DISSOLUTION TESTING SHOULD BE PERFORMED.
[2] IN THE ABSENCE OF AN ESTABLISHED IN VITRO/IN VIVO CORRELATION.

EXTENDED RELEASE SOLID ORAL DOSAGE FORMS
RELEASE CONTROLLING COMPONENTS AND COMPOSITION

LEVEL	CLASSIFICATION	THERAPEUTIC RANGE	TEST DOCUMENTATION	FILING DOCUMENTATION
I	-≤ 5% W/W CHANGE BASED ON TOTAL RELEASE CONTROLLING EXCIPIENT (e.g., controlled release polymer, plasticizer) CONTENT -NO OTHER CHANGES	ALL DRUGS	-STABILITY -APPLICATION/COMPENDIAL REQUIREMENTS -NO BIOSTUDY	-ANNUAL REPORT
II	-CHANGE IN TECHNICAL GRADE AND/OR SPECIFICATIONS -≤10% W/W CHANGE BASED ON TOTAL RELEASE CONTROLLING EXCIPIENT (e.g., controlled release polymer, plasticizer) CONTENT -NO OTHER CHANGES	NON-NARROW	-NOTIFICATION & UPDATED BATCH RECORD -STABILITY -APPLICATION/COMPENDIAL REQUIREMENTS PLUS MULTI-POINT DISSOLUTION PROFILES IN THREE OTHER MEDIA (e.g., WATER, 0.1N HCL, AND USP BUFFER MEDIA AT pH 4.5 AND 6.8) UNTIL ≥80% OF DRUG RELEASED OR AN ASYMPTOTE IS REACHED[1] -APPLY SOME STATISTICAL TEST (F2 TEST) FOR COMPARING DISSOLUTION PROFILES[2] -NO BIOSTUDY	-PRIOR APPROVAL SUPPLEMENT
		NARROW	-UPDATED BATCH RECORD -STABILITY -APPLICATION/COMPENDIAL (PROFILE) REQUIREMENTS -BIOSTUDY OR IVIVC[1]	-PRIOR APPROVAL SUPPLEMENT
III	->10% W/W CHANGE BASED ON TOTAL RELEASE CONTROLLING EXCIPIENT (e.g., controlled release polymer, plasticizer) CONTENT	ALL DRUGS	-UPDATED BATCH RECORD -STABILITY -APPLICATION/COMPENDIAL (PROFILE) REQUIREMENTS -BIOSTUDY OR IVIVC[1]	-PRIOR APPROVAL SUPPLEMENT

[1] IN THE PRESENCE OF AN ESTABLISHED IN VITRO/IN VIVO CORRELATION ONLY APPLICATION/COMPENDIAL DISSOLUTION TESTING SHOULD BE PERFORMED.
[2] IN THE ABSENCE OF AN ESTABLISHED IN VITRO/IN VIVO CORRELATION.

EXTENDED RELEASE SOLID ORAL DOSAGE FORMS
SITE CHANGE

LEVEL	CLASSIFICATION	THERAPEUTIC RANGE	TEST DOCUMENTATION	FILING DOCUMENTATION
I	-SINGLE FACILITY -COMMON PERSONNEL -NO OTHER CHANGES	ALL DRUGS	-APPLICATION/COMPENDIAL REQUIREMENTS -NO BIOSTUDY	-ANNUAL REPORT
II	-SAME CONTIGUOUS CAMPUS -COMMON PERSONNEL -NO OTHER CHANGES	ALL DRUGS	-IDENTIFICATION AND DESCRIPTION OF SITE CHANGE, AND UPDATED BATCH RECORD -NOTIFICATION OF SITE CHANGE -STABILITY -APPLICATION/COMPENDIAL REQUIREMENTS PLUS MULTI-POINT DISSOLUTION PROFILES IN THREE OTHER MEDIA (e.g., WATER, 0.1N HCL, AND USP BUFFER MEDIA AT pH 4.5 AND 6.8) UNTIL ≥80% OF DRUG RELEASED OR AN ASYMPTOTE IS REACHED[1] -APPLY SOME STATISTICAL TEST (F2 TEST) FOR COMPARING DISSOLUTION PROFILES[2] -NO BIOSTUDY	-CHANGES BEING EFFECTED SUPPLEMENT
III	-DIFFERENT CAMPUS -DIFFERENT PERSONNEL	ALL DRUGS	-NOTIFICATION OF SITE CHANGE -UPDATED BATCH RECORD -STABILITY -APPLICATION/COMPENDIAL (PROFILE) REQUIREMENTS -BIOSTUDY OR IVIVC[1]	-PRIOR APPROVAL SUPPLEMENT

[1] IN THE PRESENCE OF AN ESTABLISHED IN VITRO/IN VIVO CORRELATION ONLY APPLICATION/COMPENDIAL DISSOLUTION TESTING SHOULD BE PERFORMED.
[2] IN THE ABSENCE OF AN ESTABLISHED IN VITRO/IN VIVO CORRELATION.

EXTENDED RELEASE SOLID ORAL DOSAGE FORMS
SCALE-UP/SCALE-DOWN

LEVEL	CLASSIFICATION	CHANGE	TEST DOCUMENTATION	FILING DOCUMENTATION
I	-SCALE-UP OF BIO-BATCH(S) OR PIVOTAL CLINICAL BATCH(S) -NO OTHER CHANGES	≤10X (ALL DRUGS)	-UPDATED BATCH RECORD -STABILITY -APPLICATION/COMPENDIAL REQUIREMENTS -NO BIOSTUDY	-ANNUAL REPORT
II	-SCALE-UP OF BIO-BATCH(S) OR PIVOTAL CLINICAL BATCH(S) -NO OTHER CHANGES	>10X (ALL DRUGS)	-UPDATED BATCH RECORD -STABILITY -APPLICATION/COMPENDIAL REQUIREMENTS PLUS MULTI-POINT DISSOLUTION PROFILES IN THREE OTHER MEDIA (e.g., WATER, 0.1N HCL, AND USP BUFFER MEDIA AT pH 4.5 AND 6.8) UNTIL ≥80% OF DRUG RELEASED OR AN ASYMPTOTE IS REACHED[1] -APPLY SOME STATISTICAL TEST (F2 TEST) FOR COMPARING DISSOLUTION PROFILES[2] -NO BIOSTUDY	-CHANGES BEING EFFECTED SUPPLEMENT

[1] IN THE PRESENCE OF AN ESTABLISHED IN VITRO/IN VIVO CORRELATION ONLY APPLICATION/COMPENDIAL DISSOLUTION TESTING SHOULD BE PERFORMED.
[2] IN THE ABSENCE OF AN ESTABLISHED IN VITRO/IN VIVO CORRELATION.

EXTENDED RELEASE SOLID ORAL DOSAGE FORMS
MANUFACTURING - EQUIPMENT

LEVEL	CLASSIFICATION	CHANGE	TEST DOCUMENTATION	FILING DOCUMENTATION
I	-EQUIPMENT CHANGES -NO OTHER CHANGES (ALL DRUGS)	-ALTERNATE EQUIPMENT OF SAME DESIGN AND PRINCIPLE -AUTOMATED EQUIPMENT	-UPDATED BATCH RECORD -STABILITY -APPLICATION/COMPENDIAL REQUIREMENTS -NO BIOSTUDY	-ANNUAL REPORT
II	-EQUIPMENT CHANGES -NO OTHER CHANGES (ALL DRUGS)	-CHANGE TO EQUIPMENT OF A DIFFERENT DESIGN AND OPERATING PRINCIPLE	-UPDATED BATCH RECORD -STABILITY -APPLICATION/COMPENDIAL REQUIREMENTS PLUS MULTI-POINT DISSOLUTION PROFILES IN THREE OTHER MEDIA (e.g., WATER, 0.1N HCL, AND USP BUFFER MEDIA AT pH 4.5 AND 6.8) UNTIL ≥80% OF DRUG RELEASED OR AN ASYMPTOTE IS REACHED[1] -APPLY SOME STATISTICAL TEST (F2 TEST) FOR COMPARING DISSOLUTION PROFILES[2] -NO BIOSTUDY	-PRIOR APPROVAL SUPPLEMENT

[1] IN THE PRESENCE OF AN ESTABLISHED IN VITRO/IN VIVO CORRELATION ONLY APPLICATION/COMPENDIAL DISSOLUTION TESTING SHOULD BE PERFORMED.
[2] IN THE ABSENCE OF AN ESTABLISHED IN VITRO/IN VIVO CORRELATION.

EXTENDED RELEASE SOLID ORAL DOSAGE FORMS
MANUFACTURING - PROCESSING

LEVEL	CLASSIFICATION	CHANGE	TEST DOCUMENTATION	FILING DOCUMENTATION
I	-PROCESSING CHANGES AFFECTING THE NON-RELEASE CONTROLLING EXCIPIENTS AND/OR THE RELEASE CONROLLING EXCIPIENTS -NO OTHER CHANGES	-ADJUSTMENT OF EQUIPMENT OPERATING CONDITIONS (e.g. mixing times, operating speeds, etc.) -WITHIN APPROVED APPLICATION RANGES	-UPDATED BATCH RECORD -APPLICATION/COMPENDIAL REQUIREMENTS -NO BIOSTUDY	-ANNUAL REPORT
II	-PROCESSING CHANGES AFFECTING THE NON-RELEASE CONTROLLING EXCIPIENTS AND/OR THE RELEASE CONTROLLING EXCIPIENTS -NO OTHER CHANGES	-ADJUSTMENT OF EQUIPMENT OPERATING CONDITIONS (e.g. mixing times, operating speeds, etc.) -BEYOND APPROVED APPLICATION RANGES	-UPDATED BATCH RECORD -STABILITY -APPLICATION/COMPENDIAL REQUIREMENTS PLUS MULTI-POINT DISSOLUTION PROFILES IN THREE OTHER MEDIA (e.g. WATER, 0.1N HCL, AND USP BUFFER MEDIA AT pH 4.5 AND 6.8) UNTIL $\geq$ 80% OF DRUG RELEASED OR AN ASYMPTOTE IS REACHED[1] -APPLY SOME STATISTICAL TEST (F2 TEST) FOR COMPARING DISSOLUTION PROFILES[2] -NO BIOSTUDY	-CHANGES BEING EFFECTED SUPPLEMENT
III	-PROCESSING CHANGES AFFECTING THE NON-RELEASE CONTROLLING EXCIPIENTS AND/OR THE RELEASE CONROLLING EXCIPIENTS	-CHANGE IN THE TYPE OF PROCESS USED (e.g. from wet granulation to direct compression)	-UPDATED BATCH RECORD -STABILITY -APPLICATION/COMPENDIAL (PROFILE) REQUIREMENTS -BIOSTUDY OR IVIVC[1]	-PRIOR APPROVAL SUPPLEMENT

[1] IN THE PRESENCE OF AN ESTABLISHED IN VITRO/IN VIVO CORRELATION ONLY APPLICATION/COMPENDIAL DISSOLUTION TESTING SHOULD BE PERFORMED.

[2] IN THE ABSENCE OF AN ESTABLISHED IN VITRO/IN VIVO CORRELATION.

DELAYED RELEASE SOLID ORAL DOSAGE FORMS
NON-RELEASE CONTROLLING COMPONENTS AND COMPOSITION

LEVEL	CLASSIFICATION	THERAPEUTIC RANGE	TEST DOCUMENTATION	FILING DOCUMENTATION
I	-COMPLETE OR PARTIAL DELETION OF COLOR/FLAVOR -CHANGE IN INKS, IMPRINTS -UPTO SUPAC-IR LEVEL 1 EXCIPIENT RANGES -NO OTHER CHANGES	ALL DRUGS	-STABILITY -APPLICATION/COMPENDIAL REQUIREMENTS -NO BIOSTUDY	-ANNUAL REPORT
II	-CHANGE IN TECHNICAL GRADE AND/OR SPECIFICATIONS -HIGHER THAN SUPAC-IR LEVEL 1 BUT LESS THAN LEVEL 2 EXCIPIENT RANGES -NO OTHER CHANGES	ALL DRUGS	-NOTIFICATION & UPDATED BATCH RECORD -STABILITY -APPLICATION/COMPENDIAL REQUIREMENTS PLUS MULTI-POINT DISSOLUTION PROFILES IN ADDITIONAL BUFFER STAGE TESTING (e.g., USP BUFFER MEDIA AT pH 4.5-7.5) UNDER STANDARD AND INCREASED AGITATION CONDITIONS UNTIL ≥80% OF DRUG RELEASED OR AN ASYMPTOTE IS REACHED[1] -APPLY SOME STATISTICAL TEST (F2 TEST) FOR COMPARING DISSOLUTION PROFILES[2] -NO BIOSTUDY	-PRIOR APPROVAL SUPPLEMENT
III	-HIGHER THAN SUPAC-IR LEVEL 2 EXCIPIENT RANGES	ALL DRUGS	-UPDATED BATCH RECORD -STABILITY -APPLICATION/COMPENDIAL (PROFILE) REQUIREMENTS -BIOSTUDY OR IVIVC[1]	-PRIOR APPROVAL SUPPLEMENT

[1] IN THE PRESENCE OF AN ESTABLISHED IN VITRO/IN VIVO CORRELATION ONLY APPLICATION/COMPENDIAL DISSOLUTION TESTING SHOULD BE PERFORMED.
[2] IN THE ABSENCE OF AN ESTABLISHED IN VITRO/IN VIVO CORRELATION.

DELAYED RELEASE SOLID ORAL DOSAGE FORMS
RELEASE CONTROLLING COMPONENTS AND COMPOSITION

LEVEL	CLASSIFICATION	THERAPEUTIC RANGE	TEST DOCUMENTATION	FILING DOCUMENTATION
I	-≤5% W/W CHANGE BASED ON TOTAL RELEASE CONTROLLING EXCIPIENT (e.g., controlled release polymer, plasticizer) CONTENT -NO OTHER CHANGES	ALL DRUGS	-STABILITY -APPLICATION/COMPENDIAL REQUIREMENTS -NO BIOSTUDY	-ANNUAL REPORT
II	-CHANGE IN TECHNICAL GRADE AND/OR SPECIFICATIONS -≤10% W/W CHANGE BASED ON TOTAL RELEASE CONTROLLING EXCIPIENT (e.g., controlled release polymer, plasticizer) CONTENT -NO OTHER CHANGES	NON-NARROW	-NOTIFICATION & UPDATED BATCH RECORD -STABILITY -APPLICATION/COMPENDIAL REQUIREMENTS PLUS MULTI-POINT DISSOLUTION PROFILES IN ADDITIONAL BUFFER STAGE TESTING (e.g., USP BUFFER MEDIA AT pH 4.5-7.5) UNDER STANDARD AND INCREASED AGITATION CONDITIONS UNTIL ≥80% OF DRUG RELEASED OR AN ASYMPTOTE IS REACHED[1] -APPLY SOME STATISTICAL TEST (F2 TEST) FOR COMPARING DISSOLUTION PROFILES[2] -NO BIOSTUDY	-PRIOR APPROVAL SUPPLEMENT
		NARROW	-UPDATED BATCH RECORD -STABILITY -APPLICATION/COMPENDIAL (PROFILE) REQUIREMENTS -BIOSTUDY OR IVIVC[1]	-PRIOR APPROVAL SUPPLEMENT
III	>10% W/W CHANGE BASED ON TOTAL RELEASE CONTROLLING EXCIPIENT (e.g., controlled release polymer, plasticizer) CONTENT	ALL DRUGS	-UPDATED BATCH RECORD & STABILITY -APPLICATION/COMPENDIAL (PROFILE) REQUIREMENTS -BIOSTUDY OR IVIVC[1]	-PRIOR APPROVAL SUPPLEMENT

[1] IN THE PRESENCE OF AN ESTABLISHED IN VITRO/IN VIVO CORRELATION ONLY APPLICATION/COMPENDIAL DISSOLUTION TESTING SHOULD BE PERFORMED.
[2] IN THE ABSENCE OF AN ESTABLISHED IN VITRO/IN VIVO CORRELATION.

DELAYED RELEASE SOLID ORAL DOSAGE FORMS
SITE CHANGE

LEVEL	CLASSIFICATION	THERAPEUTIC RANGE	TEST DOCUMENTATION	FILING DOCUMENTATION
I	-SINGLE FACILITY -COMMON PERSONNEL -NO OTHER CHANGES	ALL DRUGS	-APPLICATION/COMPENDIAL REQUIREMENTS -NO BIOSTUDY	-ANNUAL REPORT
II	-SAME CONTIGUOUS CAMPUS -COMMON PERSONNEL -NO OTHER CHANGES	ALL DRUGS	-IDENTIFICATION AND DESCRIPTION OF SITE CHANGE, AND UPDATED BATCH RECORD -NOTIFICATION OF SITE CHANGE -STABILITY -APPLICATION/COMPENDIAL REQUIREMENTS PLUS MULTI-POINT DISSOLUTION PROFILES IN ADDITIONAL BUFFER STAGE TESTING (e.g., USP BUFFER MEDIA AT pH 4.5-7.5) UNDER STANDARD AND INCREASED AGITATION CONDITIONS UNTIL ≥80% OF DRUG RELEASED OR AN ASYMPTOTE IS REACHED[1] -APPLY SOME STATISTICAL TEST (F2 TEST) FOR COMPARING DISSOLUTION PROFILES[2] -NO BIOSTUDY	-CHANGES BEING EFFECTED SUPPLEMENT
III	-DIFFERENT CAMPUS -DIFFERENT PERSONNEL	ALL DRUGS	-NOTIFICATION OF SITE CHANGE -UPDATED BATCH RECORD -STABILITY -APPLICATION/COMPENDIAL (PROFILE) REQUIREMENTS -BIOSTUDY OR IVIVC[1]	-PRIOR APPROVAL SUPPLEMENT

[1] IN THE PRESENCE OF AN ESTABLISHED IN VITRO/IN VIVO CORRELATION ONLY APPLICATION/COMPENDIAL DISSOLUTION TESTING SHOULD BE PERFORMED.
[2] IN THE ABSENCE OF AN ESTABLISHED IN VITRO/IN VIVO CORRELATION.

DELAYED RELEASE SOLID ORAL DOSAGE FORMS
SCALE-UP/SCALE-DOWN

LEVEL	CLASSIFICATION	CHANGE	TEST DOCUMENTATION	FILING DOCUMENTATION
I	-SCALE-UP OF BIO-BATCH(S) OR PIVOTAL CLINICAL BATCH(S) -NO OTHER CHANGES	≤10X (ALL DRUGS)	-UPDATED BATCH RECORD -STABILITY -APPLICATION/COMPENDIAL REQUIREMENTS -NO BIOSTUDY	-ANNUAL REPORT
II	-SCALE-UP OF BIO-BATCH(S) OR PIVOTAL CLINICAL BATCH(S) -NO OTHER CHANGES	>10X (ALL DRUGS)	-UPDATED BATCH RECORD -STABILITY -APPLICATION/COMPENDIAL REQUIREMENTS PLUS MULTI-POINT DISSOLUTION PROFILES IN ADDITIONAL BUFFER STAGE TESTING (e.g., USP BUFFER MEDIA AT pH 4.5-7.5) UNDER STANDARD AND INCREASED AGITATION CONDITIONS UNTIL ≥80% OF DRUG RELEASED OR AN ASYMPTOTE IS REACHED[1] -APPLY SOME STATISTICAL TEST (F2 TEST) FOR COMPARING DISSOLUTION PROFILES[2] -NO BIOSTUDY	-CHANGES BEING EFFECTED SUPPLEMENT

[1] IN THE PRESENCE OF AN ESTABLISHED IN VITRO/IN VIVO CORRELATION ONLY APPLICATION/COMPENDIAL DISSOLUTION TESTING SHOULD BE PERFORMED.
[2] IN THE ABSENCE OF AN ESTABLISHED IN VITRO/IN VIVO CORRELATION.

DELAYED RELEASE SOLID ORAL DOSAGE FORMS
MANUFACTURING - EQUIPMENT

LEVEL	CLASSIFICATION	CHANGE	TEST DOCUMENTATION	FILING DOCUMENTATION
I	-EQUIPMENT CHANGES -NO OTHER CHANGES (ALL DRUGS)	-ALTERNATE EQUIPMENT OF SAME DESIGN AND PRINCIPLE -AUTOMATED EQUIPMENT	-UPDATED BATCH RECORD -STABILITY -APPLICATION/COMPENDIAL REQUIREMENTS -NO BIOSTUDY	-ANNUAL REPORT
II	-EQUIPMENT CHANGES -NO OTHER CHANGES (ALL DRUGS)	-CHANGE TO EQUIPMENT OF A DIFFERENT DESIGN AND OPERATING PRINCIPLE	-UPDATED BATCH RECORD -STABILITY -APPLICATION/COMPENDIAL REQUIREMENTS PLUS MULTI-POINT DISSOLUTION PROFILES IN ADDITIONAL BUFFER STAGE TESTING (e.g., USP BUFFER MEDIA AT pH 4.5-7.5) UNDER STANDARD AND INCREASED AGITATION CONDITIONS UNTIL ≥80% OF DRUG RELEASED OR AN ASYMPTOTE IS REACHED[1] -APPLY SOME STATISTICAL TEST (F2 TEST) FOR COMPARING DISSOLUTION PROFILES[2] -NO BIOSTUDY	-PRIOR APPROVAL SUPPLEMENT

[1] IN THE PRESENCE OF AN ESTABLISHED IN VITRO/IN VIVO CORRELATION ONLY APPLICATION/COMPENDIAL DISSOLUTION TESTING SHOULD BE PERFORMED.

[2] IN THE ABSENCE OF AN ESTABLISHED IN VITRO/IN VIVO CORRELATION.

DELAYED RELEASE SOLID ORAL DOSAGE FORMS
MANUFACTURING - PROCESSING

LEVEL	CLASSIFICATION	CHANGE	TEST DOCUMENTATION	FILING DOCUMENTATION
I	-PROCESSING CHANGES AFFECTING THE NON-RELEASE CONTROLLING EXCIPIENTS AND/OR THE RELEASE CONTROLLING EXCIPIENTS -NO OTHER CHANGES	-ADJUSTMENT OF EQUIPMENT OPERATING CONDITIONS (e.g. mixing times, operating speeds, etc.) -WITHIN APPROVED APPLICATION RANGES	-UPDATED BATCH RECORD -APPLICATION/COMPENDIAL REQUIREMENTS -NO BIOSTUDY	-ANNUAL REPORT
II	-PROCESSING CHANGES AFFECTING THE NON-RELEASE CONTROLLING EXCIPIENTS AND/OR THE RELEASE CONTROLLING EXCIPIENTS -NO OTHER CHANGES	-ADJUSTMENT OF EQUIPMENT OPERATING CONDITIONS (e.g. mixing times, operating speeds, etc.) -BEYOND APPROVED APPLICATION RANGES	-UPDATED BATCH RECORD -STABILITY -APPLICATION/COMPENDIAL REQUIREMENTS PLUS MULTI-POINT DISSOLUTION PROFILES IN ADDITIONAL BUFFER STAGE TESTING (e.g., USP BUFFER MEDIA AT pH 4.5-7.5) UNDER STANDARD AND INCREASED AGITATION CONDITIONS UNTIL $\geq$ 80% OF DRUG RELEASED OR AN ASYMPTOTE IS REACHED[1] -APPLY SOME STATISTICAL TEST (F2 TEST) FOR COMPARING DISSOLUTION PROFILES[2] -NO BIOSTUDY	-CHANGES BEING EFFECTED SUPPLEMENT
III	-PROCESSING CHANGES AFFECTING THE NON-RELEASE CONTROLLING EXCIPIENTS AND/OR THE RELEASE CONROLLING EXCIPIENTS	-CHANGE IN THE TYPE OF PROCESS USED (e.g. from wet granulation to direct compression)	-UPDATED BATCH RECORD -STABILITY -APPLICATION/COMPENDIAL (PROFILE) REQUIREMENTS -BIOSTUDY OR IVIVC[1]	-PRIOR APPROVAL SUPPLEMENT

[1] IN THE PRESENCE OF AN ESTABLISHED IN VITRO/IN VIVO CORRELATION ONLY APPLICATION/COMPENDIAL DISSOLUTION TESTING SHOULD BE PERFORMED.
[2] IN THE ABSENCE OF AN ESTABLISHED IN VITRO/IN VIVO CORRELATION.