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A REVIEW ON SUPAC GUIDANCE FOR MODIFIED RELEASE SOLID ORALDOSAGE FORMS

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ABSTRACT
This is the guidance about the level of changes, recommended chemistry, manufacturing and control tests for each level of change. Also included in vitro dissolution tests and/or in vivo bioequivalence tests for each level of changes. Further guidance on documentation that supports the each level of change.Also included in stability of the documentation that support each level of change.

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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 post approval 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 post approval changes.

GENERAL STABILITY CONSIDERATIONS[2]

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.

COMPONENTS AND COMPOSITION – NONRELEASE CONTROLLING EXCIPIENT[3,6]

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.

Level 1 Change

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 Dosage Form	Percent (w/w) Out Of Total weight
Target	
• Filler	±5
• Disintegrate 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%. 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

Test Documentation

Chemistry documentation Application/compendial product release requirements.

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

Dissolution documentation

None beyond application/compendial requirements.

Bioequivalence documentation

None.

Filing Documentation

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

Level 2 Change

Definition of Level

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

Examples:

A. change in the technical grade and/or specifications of a non release controlling excipient.

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 equal to the following percent ranges (which represent a two-fold increase over level 1 changes)

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.

Level 2

Nonrelease Controlling Excipient	Percent Excipient (w/w) Out Of Total Target Dosage Form Weight
Filler	±10
Disintegrate 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

Example 2

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.

Test documentation

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.

Dissolution documentation :[8]

Extended release: In addition to application/compandial release requirements, Multipoint dissolution profiles, 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. Adequate sampling at 1,2 and 4 hrs and every two hours thereafter until either 80% of the drug from the drug product is released Surfactant (appropriate justification).

Delayed release: In addition to application/compandial release requirements, dissolution test in 0.1 N HCL for 2 hrs followed by testing in USP buffer media in the range of pH 4.5-

7.5 under standard test condition & two agitation speeds using the application/compandial test apparatus . 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.

All modified release solid dosage form:[5]

In the presence of an established in vivo/in vitro correlation, only application/compendial dissolution testing need be performed 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 2equation) 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.

Bioequivalence documentation – none

Filing Documentation:

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

Level 3 Change

Definition of Level

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

Example:

Changes in the non release controlling excipient range beyond those listed in Section III.B.1.

The total weight of the dosage form may be within or outside the approved original application range.

Test Documentation

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.

Dissolution documentation: same as level 2 change

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).

Filing Documentation

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

COMPONENTS AND COMPOSITION —RELEASE CONTROLLING EXCIPIENT[3,6]

This section of the guidance focuses on changes in release controlling excipients in the drug product.

Level 1 Change

Definition of Level

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

Example:

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.

Test Documentation

Chemistry documentation

Application/compendial product release requirements.

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

Dissolution documentation

None beyond application/compendial requirements.

Bioequivalence documentation: none

Filing Documentation

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

Level 2 Change

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.

Examples:

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

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.

Test Documentation

Chemistry documentation

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

Stability: No narrow 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.

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.

Dissolution documentation

No narrow therapeutic range drugs : same as nonrelease controlling excipients

No narrow therapeutic range drugs : same as nonrelease controlling excipients (Extended release and Delayed release)

Bioequivalence documentation

No narrow therapeutic range drugs: None.

No 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.

Filing Documentation

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

Level 3 Change

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:

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

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 (greater than 10%)

Test Documentation

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.

Dissolution documentation: same as non release controlling excipients (Extended release and Delayed release)

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.

Filing Documentation

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

SITE CHANGES[4]

Site changes consist (for both company-owned and contract manufacturing facilities.)

- Changes in location of the site of manufacture,
- Packaging operations,
- And/or analytical testing laboratory

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.

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.

Level 1 Change

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 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.

Test Documentation

Chemistry documentation

None beyond application/compendial product release requirements.

Dissolution documentation

None beyond application / compendial release requirements.

Bioequivalence documentation

None.

Filing Documentation Annual report.

Level 2 Change

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.

Test Documentation

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.

Dissolution documentation: (same as nonrelease controlling excipients)

Bioequivalence documentation

None.

Filing Documentation

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

Level 3 Change

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.

Test Documentation

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.

Dissolution documentation : same as nonrelease controlling excipients (Extended release and Delayed release)

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).

Filing Documentation

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

CHANGES IN BATCH SIZE (SCALE- UP/SCALE-DOWN)[9]

Post approval 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.

Level 1 Change

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 menufacturing procedures, are used on the test batch(es) and on the full-scale production batch(es).

Test Documentation

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.

Dissolution documentation

None beyond application/compendial release requirements.

Bioequivalence documentation: None.

Filing Documentation

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

Level 2 Change

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).

Test Documentation

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.

Dissolution documentation (same as nonrelease controlling excipients)
Bioequivalence documentation
None.
Filing Documentation
Changes Being Effected supplement (all information including accelerated stability data); annual report (long-term stability data).

MANUFACTURING PROCESS CHANGES[7]

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.

Level 1 Change
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.
Test Documentation
Chemistry documentation
None beyond application/compendial product release requirements.
Notification of the change and submission of the updated executed batch records. Dissolution documentation
None beyond application/compendial release requirements.
Bioequivalence documentation
None.
Filing Documentation Annual report.

Level 2 Change
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.
Dissolution documentation (same as nonrelease controlling excipients)
Bioequivalence documentation
None.
Filing Documentation
Changes Being Effected supplement (all information including accelerated stability data); annual report (long-term stability data).

Level 3 Change
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.
Test Documentation
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 productions
Batches reported in annual report.

Dissolution documentation: same as nonrelease controlling excipients
(Extended release and Delayed release)
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).
Filing Documentation
Prior approval supplement (all information including accelerated stability data); annual report (long-term stability data).

REFERENCES

1) FDA, "Interim Policy on Exceptions to the Batch-Size and Production Condition Requirements for Non-Antibiotic, Solid, Oral-Dosage Form Drug Products Supporting Proposed ANDA's" Policy and Procedure Guide #22-90, September 13, 1990. Office of Generic Drugs, CDER, September 13, 1990.
2) FDA, Guideline for Submitting Documentation for the Manufacture of and Controls for Drug Products, February 1987.
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.
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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: Scale up of Oral Extended-Release Dosage Forms," Pharmaceutical Research, 10(12): 1800-1805, 1993.

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