A. 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)].

B. Contiguous Campus

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

C. Dissolution Testing

Case A: Dissolution of Q = 85% in 15 minutes in 900 milliliters (mL) of 0.1N hydrochloride (HCl), using the United States Pharmacopeia (USP) <711> Apparatus 1 at 100 revolutions per minute (rpm) or Apparatus 2 at 50 rpm.

Case B: Multi-point dissolution profile in the application/compendial medium at 15, 30, 45, 60, and 120 minutes or until an asymptote is reached for the proposed and currently accepted formulation.

Case C: Multi-point dissolution profiles performed in water, 0.1N HCl, and USP buffer media at pH 4.5, 6.5, and 7.5 (five separate profiles) for the proposed and currently accepted formulations. Adequate sampling should be performed at 15, 30, 45, 60, and 120 minutes until either 90% of drug from the drug product is dissolved or an asymptote is reached. A surfactant may be used with appropriate justification.

date / /

← نكمل حكي عن الـ Contiguous Campus مثلًا الحكمة كشركة، وغيرها من الشركات هدول بيعتبروا كتنال على non-contiguous cam .. كل واحد إله Site خاص فيه و GMP خاص فيه برضه ..

← ذكرت الدكتورة الـ Level يلي ذكرتلك ياهم بالتفريغ السّابق وحكت .. لو شركة الحكمة كان عندها مبنيين بنفس العكل مثلًا .. لو بدهم ينقلوا من هاد المبنى للتاني هاد "تحت" Level one يلي هو not effect Quality .. لو بدهم ينقلوا على موقعهم يلي بكان تاني مثلًا على موقع بلد أو مدينة زي السلط مثلًا هاد بسميه Level 2 .. لو بدهم ينقلوا لبرّا الأردن .. للهند مثلًا .. هاد Level 3 ..

⇒ Dissolution testing

عندي ٣ أنواع من الـ Dissolution

* **Case A** .. Dissolution

← مطلوب منك الـ Q = %85 في media مثل الـ HCL على 50 rpm .. حتى لو الـ mongraph بده تشغلي على 75 rpm لا تخشي إلها على 50 .. لأنه كلما قل rpm يبين عندك الـ Dalechive أكتر .. طبعًا بالـ Case A بدك تقل single point

يعني عند نقطة واحدة.

* **Case B** ...

← بدك تقل profile، يعني multi-point يبلش من 15 min، وعادة بوخذوا من دقيقة أقل .. ممكن 5 min .. عومًا .. أول ساعة بدك توخذ نقطة كل ربع ساعة يعني 15 .. 30 .. 45 .. 60 بعد الساعة .. كل ساعة توخذ .. مثلًا 15 .. 30 .. 45 .. 60 .. 120 ..

* **Case C**

← بدك تقل الـ Dissolution على 5 media مختلفة .. تغطي كل الـ pH مثلًا 6.5, 6.5, 7.5 .. والـ rpm تكون أدنى ما يكون ..

D. Drug Product

A drug product is a finished dosage form (e.g., tablet, capsule, or solution) 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 tablets, chewable tablets, capsules, and soft gelatin capsules.

E. 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)].

F. Equipment

Automated or non-automated, mechanical or non-mechanical equipment used to produce the drug product, including equipment used to package the drug product.

G. Formulation

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

H. Justification

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

I. New Drug Substance

Any substance that, when used in the manufacture, processing, or packing of a drug, causes that drug to be a new drug, but does not include intermediates used in the synthesis of such substance [21 CFR 310.3(g)].

J. Operating Principle

Rules or concepts governing the operation of the system.

K. 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 (see the FEDERAL REGISTER of Thursday, September 22, 1994, 59 FR 48754-59).

L. Process

A series of operations and/or actions used to produce a desired result.

M. Ranges

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

N. Same

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

O. Scale-up

The process of increasing the batch size.

P. Scale-down

The process of decreasing the batch size.

Q. Similar

Having a general likeness.

R. Significant body of information

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.

S. 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 the production phase. Validation necessarily includes process qualification (the qualification of materials, equipment, systems, buildings, and personnel), but it also includes the control of the entire processes for repeated batches or runs.

III. COMPONENTS AND COMPOSITION

This section of the guidance focuses on changes in excipients in the drug product. Changes in the amount of 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.

A. Level 1 Changes

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 excipients, expressed as percentage (w/w) of total formulation, less than or equal to the following percent ranges:

date / /

* pilot Scale

← لما تيجي تصنع RND 500g من ال powder أو 700g بعدها تبلش تصنع 1Kg , 2Kg ..... الخ .. بعدين بدك تصنع stabelity batch يلي تقدر تقريبًا 10000 uni على سبيل المثال .. هاد ما تقدر تصنعه بمختبرات RND تصنعهم بشي اسمه pilot .. يلي تشغيل تجريبي بس ال pilot بالمصنع بعتبر place .. بالتالي عنا pilot batch يلي هي التشغيل التجريبي ... وفي عنا مصنع صغير اسمه pilot تابع للـ RND بس معاه GMP ... فيه ماكينات .. وتكون صغيرة .. دوبها تسع لـ 30 كابسول مثلًا .. غالبًا ال pilot هاي يا لحق نجرب أدوية ونصنعها بكميات قليلة .. أو مثلًا للأدوية يلي يكون تصنيعها أصلًا قليل، ال market تاعها كثير ضيق ...

→ Components and Compositions

Level 1 Changes

← متذكرين لما حكينا عن ال root Analysis وإنه جبنا Starch وغيرناه وصدري شو وقللنا من التركيز تاع ال Starch

هاي هي ال changes يلي نقوم فيها .. فإحنا نغير على ال Compositions من الأمثلة على ال Level 1 .. يلي هو Deletion أو ال partial Deletion أو Addtion طبعًا الإضافة يعني إنك تزيد التركيز مو إنه تروح تضيف مادة ما هاش دخل .. مثلًا بالنسبة للـ Deletion من الأشياء المسموح لك تعملها حذف هي الألوان النكهات (flavor)، أو ال printing ink ...

النسب المسموح إلي أغير فيهم ب level 1

EXCIPIENT	PERCENT EXCIPIENT (w/w) OUT OF TOTAL TARGET DOSAGE FORM WEIGHT
Filler	±5
Disintegrant	
Starch	±3
Other	±1
Binder	±0.5
Lubricant	
Calcium (Ca) or Magnesium (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 excipient changes should not be more than 5%. (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 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).

The components (active and excipients) in the formulation should have numerical targets which 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 approved target composition and not on previous Level 1 changes in the composition.

2. Test Documentation

a. Chemistry Documentation

Application/compendial release requirements and stability testing.

Stability testing: one batch on long-term stability data reported in annual report.

b. Dissolution Documentation

None beyond application/compendial requirements.

c. *In Vivo* Bioequivalence Documentation

None.

3. Filing Documentation

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

B. Level 2 Changes

1. Definition of Level

Level 2 changes are those that could have a significant impact on formulation quality and performance. Tests and filing documentation for a Level 2 change vary depending on three factors: therapeutic range, solubility, and permeability. Therapeutic range is defined as either narrow or non-narrow. A list of narrow therapeutic range drugs is provided in Appendix A. Drug solubility and drug permeability are defined as either low or high. Solubility is calculated based on the minimum concentration of drug, milligram/milliliter (mg/mL), in the largest dosage strength, determined in the physiological pH range (pH 1 to 8) and

temperature (37 ± 0.5°C). High solubility drugs are those with a dose/solubility volume of less than or equal to 250 mL. (Example: Compound A has as its lowest solubility at 37 ± 0.5°C, 1.0 mg/mL at pH 7, and is available in 100 mg, 200 mg and 400 mg strengths. This drug would be considered a low solubility drug as its dose/solubility volume is greater than 250 mL (400 mg/1.0 mg/mL=400 mL). Permeability (P_e, centimeter per second) is defined as the effective human jejunal wall permeability of a drug and includes an apparent resistance to mass transport to the intestinal membrane. High permeability drugs are generally those with an extent of absorption greater than 90% in the absence of documented instability in the gastrointestinal tract, or those whose permeability attributes have been determined experimentally).

Examples:

a. Change in the technical grade of an excipient. (Example: Avicel PH102 vs. Avicel PH200.)

b. Changes in excipients, expressed as percent (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):

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 excipient changes should not change by more than 10%.

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 approved target composition and not on the composition based on previous Level 1 or Level 2 changes.

2. Test Documentation

a. Chemistry Documentation

Application/compendial release requirements and batch records.

Stability testing: 1 batch with 3 months accelerated stability data in supplement and 1 batch on long-term stability.

b. Dissolution Documentation

Case A: High Permeability, High Solubility Drugs

Dissolution of 85% in 15 minutes in 900 mL of 0.1N HCl. If a drug product fails to meet this criterion, the applicant should perform the tests described for Case B or C (below).

Case B: Low Permeability, High Solubility Drugs

Multi-point dissolution profile should be performed in the application/compendial medium at 15, 30, 45, 60 and 120 minutes or until an asymptote is reached. The dissolution profile of the proposed and currently used product formulations should be similar.

Case C: High Permeability, Low Solubility Drugs

Multi-point dissolution profiles should be performed in water, 0.1 N HCl, and USP buffer media at pH 4.5, 6.5, and 7.5 (five separate profiles) for the proposed and currently accepted formulations. Adequate sampling should be performed at 15, 30, 45, 60, and 120 minutes until either 90% of drug from the drug product is dissolved or an asymptote is reached. A surfactant may be used, but only with appropriate justification. The dissolution profile of the proposed and currently used product formulations should be similar.

c. *In Vivo* Bioequivalence Documentation

None: if the situation does not meet the description in Case A, Case B or Case C, refer to Level 3 changes.

3. Filing Documentation

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

C. Level 3 Changes

1. Definition of Level

Level 3 changes are those that are likely to have a significant impact on formulation quality and performance. Tests and filing documentation vary depending on the following three factors: therapeutic range, solubility, and permeability.

Examples:

a. Any qualitative and quantitative excipient changes to a narrow therapeutic drug beyond the ranges noted in Section III.A.1.b.

b. All other drugs not meeting the dissolution criteria under Section III.B.2.b.

c. Changes in the excipient ranges of low solubility, low permeability drugs beyond those listed in Section III.A.1.b.

d. Changes in the excipient ranges of all drugs beyond those listed in Section III.B.1.b.

2. Test Documentation

a. Chemistry Documentation

Application/compendial release requirements and batch records.

Significant body of information available:

One batch with three months accelerated stability data reported in supplement; one batch on long-term stability data reported in annual report.

Significant body of information not available:

Up to three batches with three months accelerated stability data reported in

date / /

→ Level "2" two

← شفتوا التراكيز يلي ذكرناهم بـ Level 1، هون نضربهم بـ X2 .. التركيز الضعف جهار ..

انزلوا لصفحة 10 عند Test Documentation .. بدك تعمل على هاد الـ Test + Level 1batch بدك تعمل Stability testing الـ 1batch أو بدك Long term .. Case A جهارها accelerated 3 month ..

هيدا هو الـ Dissolution مختلف .. حسب الـ Class تبع الـ Drug، يعني Class 1 .. high Solubility, high perma Class 2 مختلف .. و 3 مختلف .. إلخ

فإذا كان الـ Drug عندي Class 1 .. نطبق Case A .. Class 2 .. Case B .. وهكذا

بهاد الـ Level 2 موجود بس في حالة الرسوب لـ Test ..

→ Level 3

← هون راح نحتاج لـ bioequivalence يا شباب .. ما حكيت عنه شي تاني.

supplement; one batch on long-term stability data reported in annual report.

b. Dissolution Documentation

Case B dissolution profile as described in Section III.B.2.b.

c. *In Vivo* Bioequivalence Documentation

Full bioequivalence study. The bioequivalence study may be waived with an acceptable *in vivo/in vitro* correlation has been verified.

3. Filing Documentation

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

IV. SITE CHANGES

Site changes consist of changes in location of the site of manufacture for both company-owned and contract manufacturing facilities and do not include any scale-up changes, changes in manufacturing (including process and/or equipment), or changes in components or composition. Scale-up is addressed in Section V of this guidance. New manufacturing locations should have a satisfactory current Good Manufacturing Practice (CGMP) inspection.

A. Level 1 Changes

1. Definition of Level

Level 1 changes consist of site changes within a single facility where the same equipment, standard operating procedures (SOP's), environmental conditions (e.g., temperature and humidity) and controls, and personnel common to both manufacturing sites are used, and where no changes are made

date / /

→ Site Changes

← إنك تشتغل بهاد الحكي عشان إنك تحكيه .. مخليًا لما يكون عندك كارثة بالإنتاج الـbatch يبلغ وقدره بدك توخذ قرار .. بدك تطبق كل المهارات يلي عندك .. ويكون قرارك صح .. بحيث ما تكب شي.

A. Level "1" ذكرناه قبل .. كل شي نفس الشي .. زي مبنى الصيدلة كل شي بمكان واحد. ←

B. Level "2" نفس الشركة ولكن Site بمكان مختلف بنفس البلد

C. Level "3" تابعين لنفس الشركة ولكن ببلد مختلفة. كل شي مختلف

→ Batch Size

الحد تلعنا 100000 وحدة، الـ guidline ما يخطي أي تغيير تحت الـ 10 الآلف وحدة يعني إنت لو عندك 50 ألف وحدة رفعتها لـ 70 عادي .. هيك لـ 100 الـ Tablet هي الوحدة ..

→ Manufacturing

← يلي هي الـ manufacturing يلي هي Level 1, 2 .. محلك Level 1 إنت تكون processes

الآلة تاعتك غيرتها لأنها خربت مثلًا .. أما Level 2 مثلًا إنت كنت تشتغل wet granulation صرت تشتغل Dry .. وهكذا ..

to the manufacturing batch records, except for administrative information and the location of the facility. Common is defined as employees already working on the campus who have suitable experience with the manufacturing process.

2. Test Documentation

a. Chemistry Documentation

None beyond application/compendial release requirements.

b. Dissolution Documentation

None beyond application/compendial release requirements.

c. *In Vivo* Bioequivalence Documentation

None.

3. Filing Documentation

Annual report.

B. Level 2 Changes

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, SOP's, 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 manufacturing batch records, except for administrative information and the location of the facility.

2. Test Documentation

a. Chemistry Documentation

Location of new site and updated batch records. None beyond application/compendial release requirements.

One batch on long-term stability data reported in annual report.

b. Dissolution Documentation

None beyond application/compendial release requirements.

c. *In Vivo* Bioequivalence Documentation

None.

3. Filing Documentation

Changes being effected supplement; annual report (long-term stability test data).

C. Level 3 Changes

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, SOP's, environmental conditions, and controls should be used in the manufacturing process at the new site, and no changes may be made to the manufacturing batch records except for administrative information, location and language translation, where needed.

2. Test Documentation

a. Chemistry Documentation

Location of new site and updated batch records.

Application/compendial release requirements.

Stability:

Significant body of data available:

One batch with three months accelerated stability data reported in supplement; one batch on long-term stability data reported in annual report.

Significant body of data not available:

Up to three batches with three months accelerated stability data reported in supplement; up to three batches on long- term stability data reported in annual report.

b. Dissolution Documentation

Case B: Multi-point dissolution profile should be performed in the application/compendial medium at 15, 30, 45, 60 and 120 minutes or until an asymptote is reached. The dissolution profile of the drug product at the current and proposed site should be similar.

c. *In Vivo* Bioequivalence Documentation

None.

3. Filing Documentation

Changes being effected supplement; annual report (long-term stability data).

V. 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 in the application. Scale-down below 100,000 dosage units is not covered by this guidance. All scale-up changes should be properly validated and, where needed, inspected by appropriate agency personnel.

A. Level 1 Changes

1. Definition of Level

Change in batch size, up to and including a factor of 10 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 (are) manufactured in full compliance with CGMP's; and 3) the same standard operating procedures (SOP's) 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 release requirements. Notification of change and submission of updated batch records in annual report.

One batch on long-term stability reported in annual report.

b. Dissolution Documentation

None beyond application/compendial release requirements.

c. *In Vivo* Bioequivalence

None.

3. Filing Documentation

Annual report (long-term stability data).

B. Level 2 Changes

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 (are) manufactured in full compliance with CGMP'S; and 3) the same SOP's 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 release requirements. Notification of change and submission of updated batch records.

Stability testing: One batch with three months accelerated stability data and one batch on long-term stability.

b. Dissolution Documentation

Case B testing.

c. *In Vivo* Bioequivalence

None.

3. Filing Documentation

Changes being effected supplement; annual report (long-term stability data).

VI. MANUFACTURING

Manufacturing changes may affect both equipment used in the manufacturing process and the process itself.

A. Equipment

1. Level 1 Changes

a. Definition of Change

This category consists of: 1) change from non-automated or non-mechanical 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.

b. Test Documentation

i. Chemistry Documentation

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

Stability testing: One batch on long-term stability.

ii. Dissolution Documentation

None beyond application/compendial release requirements.

iii. *In Vivo* Bioequivalence Documentation

None.

c. Filing Documentation

Annual report (long-term stability data).

2. Level 2 Changes

a. Definition of Level

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

b. Test Documentation

i. Chemistry Documentation

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

Stability testing:

Significant body of data available:

One batch with three months accelerated stability data reported in supplement; one batch on long-term stability data reported in annual report.

Significant body of data not available:

Up to three batches with three months accelerated stability data reported in supplement; up to three batches on long-term stability data reported in annual report.

ii. Dissolution Documentation

Case C dissolution profile.

iii. *In Vivo* Bioequivalence Documentation

None.

c. Filing Documentation

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

B. Process

1. Level 1 Changes

a. Definition of Level

This category includes process changes including changes such as mixing times and operating speeds within application/validation ranges.

b. Test Documentation

i. Chemistry Documentation

None beyond application/compendial release requirements.

ii. Dissolution Documentation

None beyond application/compendial release requirements.

iii. *In Vivo* Bioequivalence Documentation

None.

c. Filing Documentation

Annual report.

2. Level 2 Changes

a. Definition of Level

This category includes process changes including changes such as mixing times and operating speeds outside of application/validation ranges.

b. Test Documentation

i. Chemistry Documentation

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

Stability testing: One batch on long-term stability.

ii. Dissolution Documentation

Case B dissolution profile.

iii. *In Vivo* Bioequivalence Documentation

None.

c. Filing Documentation

Changes being effected supplement; annual report (long-term stability data).

3. Level 3 Changes

a. 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.

b. Test Documentation

i. Chemistry Documentation

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

Stability testing:

Significant body of data available:

One batch with three months accelerated stability data reported in supplement; one batch on long-term stability data reported in annual report.

Significant body of data not available:

Up to three batches with three months accelerated stability data reported in supplement; up to three batches on long-term stability data reported in annual report.

ii. Dissolution Documentation

Case B dissolution.

iii. *In Vivo* Bioequivalence Documentation

In vivo bioequivalence study. The bioequivalence study may be waived if a suitable *in vivo/in vitro* correlation has been verified.

c. Filing Documentation

Prior approval supplement with justification; annual report (long-term stability data).

VII. *IN VITRO* DISSOLUTION

See current United States Pharmacopeia/National Formulary, section <711>, for general dissolution specifications. All profiles should be conducted on at least 12 individual dosage units.

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 R_t and T_t are the percent dissolved at each time point. An f_2 value between 50 and 100 suggests the two dissolution profiles are similar.

VIII. *IN VIVO* BIOEQUIVALENCE STUDIES

Below is a general outline of an *in vivo* bioequivalence study. It is intended as a guide and the design of the actual study may vary depending on the drug and dosage form.

A. *Objective:*

To compare the rate and extent of absorption of the drug product for which the manufacture has been changed, as defined in this guidance, to the drug product manufactured prior to the change.

B. *Design:*

The study design should be a single dose, two-treatment, two-period crossover with adequate washout period between the two phases of the study. Equal numbers of subjects should be randomly assigned to each of the two dosing sequences.

C. *Selection of Subjects:*

The number of subjects enrolled in the bioequivalence study should be determined statistically to account for the intrasubject variability and to meet the current bioequivalence interval.

D. *Procedure:*

Each subject should receive the following two treatments:

Treatment 1: Product manufactured with the proposed change.

Treatment 2: Product manufactured prior to the proposed change.

Following an overnight fast of at least 10 hours, subjects should receive either Treatments 1 or 2 above with 240 mL water. Food should not be allowed until 4 hours after dosing. Water may be allowed after the first hour. Subjects should be served standardized meals beginning at 4 hours during the study.

E. *Restrictions:*

Prior to and during each study phase, water may be allowed *ad libitum* except for 1 hour before and after drug administration. The subject should be served standardized meals and beverages at specified times. No alcohol or xanthine- or caffeine-containing foods and beverages should be consumed for 48 hours prior to each study period and until after the last blood sample is collected.

F. *Blood Sampling:*

Blood samples should be collected in sufficient volume for analysis of parent drug and active metabolite(s), if any. The sampling times should be such that it should be able to capture the C_{max} and T_{max} during the absorption period. Sampling should be carried out for at least three terminal elimination half-lives for both parent drug and active metabolite(s). Whole blood, plasma or serum, whichever is appropriate for the analytes, should be harvested promptly and samples should be frozen at -20^{o}C or -70^{o}C to maintain sample stability.

G. *Analytical Method:*

The assay methodology selected should ensure specificity, accuracy, interday and intraday precision, linearity of standard curves, and adequate sensitivity, recovery, and stability of the samples under the storage and handling conditions associated with the analytical method.

H. *Pharmacokinetic Analysis:*

From the plasma drug concentration-time data, AUC_{0-t}, AUC_{0-inf}, C_{max}, T_{max}, K_{el} and $t_{1/2}$ should be estimated.

I. *Statistical Analysis:*

Analysis of variance appropriate for a crossover design on the pharmacokinetic parameters using the general linear models procedures of SAS or an equivalent program should be performed, with examination of period, sequence and treatment effects. The 90% confidence intervals for the estimates of the difference between the test and reference least squares means for the pharmacokinetic parameters (AUC_{0-t}, AUC_{0-inf}, Cmax) should be calculated, using the two one-sided t-test procedure.

IX. REFERENCES

A. Code of Federal Regulations 210.3(b)(2) and (10), 310.3(b) and (g), and 320.1(a) and (e).

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

C. Federal Register. Vol. 59, No. 183, Thursday, September 22, 1994, pages 48754-59.

D. "Guideline for Industry: Stability Testing of New Drug Substances and Products," U.S. Department of Health and Human Services, Food and Drug Administration, September 1994.

E. "Guideline for Submitting Documentation for the Manufacture of and Controls for Drug Products," U.S. Department of Health and Human Services, Food and Drug Administration, February 1987.

F. Policy and Procedure Guide #22-90: "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",