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Scale-Up and Postapproval Changes (SUPAC) Regulations

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مثلاً بدي اصنع paracetamol tablet ← بحدد ال formula ال excepient وال process التصنيع

لـ نعمل 3 batch على parameters فنجرب (process validation) عشان أحدد أشو

ال parameters المناسبة للتصنيع ← بعد ما أتأكد أنه المستحضر فيجي stable

نعمل اشي اسمه scale-up ← عملية تصنيع المنتج بس بكميات أكبر

process validation ← التحقق من ال parameter يلي تأثر على عملية التصنيع

كل batch لـ نصنعها ← بوخذ عينات ← عشان أعمل stability testing عليها

pilote scale ← هو عشر التشغيلة الإنتاجية أو 100000 unite ← أيهما أكثر.

↓

العبقة كاملة

أو

one suppositories

أو

tablet

development عملية ال تشغيلة تجريبية بكون حجمها قليل والعالي شوي فتكون في pilot scale or Batch.
of drug.

What is SUPAC?

- In the process of **developing the new product** , the batch size used in earliest human studies **are small**.
- The sizes of the batch is **gradually increased(scale up)**.
- The scale up and the **changes made after approval** in the **composition manufacturing process** , **manufacturing equipment and change of site** have become known as scale up and post approval changes (SUPAC)
- It refers to the **FDA-recommended testing and filing actions** to be taken by a pharmaceutical firm when it changes the manufacturing processes of a drug product that **has been approved** via a New Drug Application (NDA), an Abbreviated New Drug Application (ANDA), or an Abbreviated Antibiotic Drug Application (AADA).
- The Agency has provided its recommendations to industry in the form of Guidances

Introduction

- The FDA has issued various guidance for supac changes designated as
  - SUPAC-IR (immediate release solid oral dosage form .
  - SUPAC-MR (for modified release solid oral doasage form)
  - SUPAC-SS (for non sterile semisolid dosage form including creams, ointements, gels and lotions)

level one ← هي أقل requirment يطلبها المشرع لأنه التغيرات يلي بعملها ما بتأثر على ال quality

level two ← could significant change quality ← majore التغيرات بكون

level 3 ← will significant change the quality. ← انا بتوقع تغير بشكل كبير

Guidance scope

- The guidance defines:

1. levels of change
   - Minor
   - Moderate
   - Major
2. recommended chemistry, manufacturing, and controls tests for each level of change
3. in vitro dissolution tests and/or in vivo bioequivalence tests for each level of change
4. documentation that should support the change.
5. Filling (Reporting)
   - Annual report
   - Changes being effected supplement
   - Prior approval supplement

History

- FDA issued the first of its SUPAC guidance in NOV1995
- This guidance addressed scale-up and PACs for immediate release oral solid dosage forms
- In Feb 1997,the FDA issued a letter containing the **most frequently asked questions regarding SUPAC**
- The clarification regarding stand-alone packing site changes
- The **second change** referred to post-approval analytical testing site changes

History

- In April 1998 the FDA issued the PAC-ATLS (post approval changes-analytical testing laboratory site) guidance document allowing **analytical testing laboratory site changes** for all regulated dosage form
- When making equipment changes ,the FDA's SUPAC-IR/MR immediate release and modified release solid oral dosage forms Manufacturing Equipment Addendum ,released in January 1999 has to be followed
- This addendum **lists various types of equipment** and categorises them into operating classes and subclasses

Level of changes

Likelihood of impact on formulation quality and performance

Level	Definition	Reporting
Level 1	Those changes that are **unlikely** to have any detectable impact on formulation quality and performance. change in color or flavor.	changes may be filed in an annual report release specification أكثر من ال ← ما يطلب long term stability ال batch ← يطلب فقط annual report. ← ما يطلب اخذ إذنه قبل ما أغير ← بس يخبره بال
Level 2	Changes are those that could have **significant impact** on the formulation quality and performance	• filed in a **changes being effected**(CBE) supplement or **prior approval (PA) supplement** • This **tests and filing** depends on therapeutic range ,solubility, permeability
Level 3	Those changes are likely to have **significant impact** on formulation quality and performance	• filed in PA supplement • This tests and filing documentation vary ,depending on therapeutic range, solubility, and permeability of the pharmaceutical product

Level 1 of changes

- Examples
  - **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
  - **Changes in excipients**, expressed as percentage (w/w) of total formulation, less than or equal to the following percent ranges

الأرقام حفظ

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

lactose.

Total change لازم يزيد عن 5٪

مسموحلي ازيده كمان في ٪.

ليش بغيره لأنه في بعض الـ excepient بتكون من natural resource بكون اختلاف عن الكمان باي. بجيب منه هاي الـ excepient.

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مع المحافظة على الـ mass Balance.

Test Documentation

- Chemistry Documentation
  - Application/compendial **release requirements and stability testing.**
  - Stability testing: **one batch on long-term stability data** reported in annual report.
- Dissolution Documentation
  - None beyond application/compendial requirements.
- In Vivo Bioequivalence Documentation
  - None

Filing Documentation

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

Level 2 of changes

- Examples:
  - Change in the technical **grade of an excipient** (Avicel PH102 vs. Avicel PH200.)
  - 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**)

Level 2 changes

EXCIPIENT	PERCENT EXCIPIENT (w/w) OUT OF TOTAL TARGET DOSAGE FORM WEIGHT
Filler	±10
Disintegrant	
Starch	±6
Other	±2

Level 2 changes

Binder	±1
Lubricant	
Ca or Mg Stearate	±0.5
Other	±2
Glidant	
Talc	±2
Other	±0.2
Film Coat	±2

Test Documentation

- **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**.

40°C + 75% RH in final packaging.

requirment level 3 = يعني بدو dissolution change اذا صار stability

long-term stability data أقدم annual report * أقدم تعتمد بال

depending on our drug :

- **Dissolution Documentation**

apparatus → basket

❑ **Case A**: **High Permeability, High Solubility**

– Drugs Dissolution of **85% in 15 minutes in 900 mL of 0.1N HCl.** ↳ highest dose dissolved in 250 mL solution.

– 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 min or until an **asymptote** is reached.

– The dissolution profile of the **proposed and currently** used product formulations should be similar

media

apparatus : paddle

formula behaviour

❑ 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**

Just in level 3.

- **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.

دراسة مكلفة جدًا ← عشان اثبت إنه الدواء يلي غيرت فيه

1. same bioavailability ← مكافئ للقديم (حيويًا) ← need + time
2. same extent of release.

Bioequivalent ← صعب يطلب في اقدم data ← dissolution بسب level 2 ← اذا المستحضر

Filing Documentation

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

1. 3 month accelerated. 2. dissolution. 3. bioequivalent in sublimentary.

Level 3 of changes

4. long term stability data.

- Examples:
  - Any **qualitative and quantitative** excipient changes to **a narrow therapeutic drug** beyond the ranges noted in **level 1**
  - All other drugs not meeting the dissolution criteria **under level 2 c**.
  - Changes in the excipient ranges of low solubility, low permeability drugs beyond Changes in the excipient ranges of all drugs beyond **2x level**

affecting on solubility and permiability.

Test documentation

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

Test documentation

- **Dissolution Documentation**
  - Case B dissolution profile as described in Section III.B.2.b.
- **In Vivo Bioequivalence Documentation**
  - **Full bioequivalence study.**
  - The bioequivalence study **may be waived** with an acceptable in **vivo/in vitro** correlation has been verified

← في بعض الحالات حتى في level 3 ممكن ما أعمل Bioequivalence study

rosovastaten ← وغيرت ال exceptiant فيهم ال 3 ← بالتالي بسمحلي أعمل Bioavilability

10, 20, 40 mg

ال 40 وبعفيني من ال 10, 20 بس بشروط.

Filing Documentation

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

Site changes

- It includes the changes in **location** of the site of manufacturing facilities for both company **owned** and **contract** manufacturer.
- It do not include scale up

مثال :-

level 1 ← مختبر صناعية 1 ـ صناعية 2 في كلية الهندسة .

level 2 ← مختبر في كلية الهندسة و مختبر في كلية الطب .

level 3 ← مختبر في كلية الهندسة الجامعة الهاشمية .

و مختبر في كلية الهندسة الجامعة الأردنية .

Site changes

level 1, 2
↓
same humedity, same temprature.
نفس الرطوبة ، نفس الحرارة / نفس الأدوات.

- **level 1 of changes**
- Site change **within a single facility** where **same equipment, SOP, Environment condition and common personnel**
- Test document- Chemistry, dissolution are according to compendial and In vivo BE **not required.**
- Filing the **annual report** (1)

→ Same document in excipient change in level 1.

Site changes

- **level 2 of changes**
- Site change within a **contiguous campus**, or between facilities in adjacent city blocks.
- Test documentation – level 1 + **one batch long term stability** in chemistry documentation
- Filing documentation – **annual report**

→ Continuous or unbroken manufacturing site

→ مواقع مختلفة لتصنيع الدواء ولكن نفس الإدارة نفس القوانين نفس

+ Dissolution Test.

same SOP

التواقيع →

هناك مصنعين الحكمة جنب بعض

لو شركة معينة كانت تصنع Paracetamol وعايزة تصنعه بدها تصنع دواء تاني
← بتروح تبعتلي محل ملف التصنيع الشركة اخرى بحيث تتأكد من استخدام نفس الـ raw material
ونفس ماكينات التصنيع ونفس طريقة التصنيع بس تغير مكان التصنيع ← هون عندي
↳ level 2 of change

→ not all changes 3 levels.

→ every level have the same requirments.

level 1 → 1. annual report (chemistry specification, release, dissolution)
supplemintary data ← نفس الـ specification العادية بس مطلوب مني
↳ هاي بعملها بس أعمل تغيير عشان لاخذ موافقة عليها → level 1 مش مطلوبة مني في

2. long-term stability data (shelf-life)

level 2 → 1. need supplemintary data → هون لازم أقدم معلومات تتأكد
فيه المستحضر لسه stable ولازم لاخذ موافقة قبل ما انزله ع السوق

2. accelerated data 3 months → my product stable under accelerated conditions → 1. 40°c temprature
2. 75% relative humedity.

3. dissolution data → similar عشان اثبت ان المستحضر الجديد للمستحضر القديم

← نوع ال dissolution يعتمد على نوع ال drug ← شوال solubility and permiability of active ingredient :

1. high soluble, high permiable → dissolution case A → single point in 0.1 normal HCL media.

2. low permiable, high soluble → dissolution case B → multi-point dissolution (15, 30, 45, 60, 120) minutes. → بال media باي مسجل دواي عليها

3. high permiable, low soluble → dissolution case C → dissolution in different challenging media (5 media) → dissolution.

← يطلب Bioequivelance بس في حالة مستحضري وسب

level 3 → 1. accelerated data 2. dissolution 3. Bioequivelance.

Site changes

- **Level 3 of changes**
- Site change to a **different campus**
- Test documentation
  - Chemistry documentation
  - **One batch for accelerated stability (3 Months)** + **One batch for long term stability** Or 3 batches for accelerate and long term stability
  - Dissolution testing – Case B
  - No BE required
- Filing documentation – **annual report**

Change in batch size

scale up or scale down. ← only 2 levels.

لكل التغيرات الباقية ثابتة من طريقة التصنيع

Batch size والمكان والمواد ← بس بيكي تغيير ال

- **Post approval changes** in the size of a batch from the pivotal/pilot scale biobatch material to **larger or smaller production**.

اذا ال Batch size الأصلي أقل من 100000 وبعد ما عملت scale down قل أقل ← ما تنطبق عليها هاي القوانين.

- Scale down below **1,00,000** dosage units is not covered by this guideline.

← بعد ما أقل من ال Batch صار أقل من 100000 صعب التطبيق

- Scale up changes should be properly **validated** and if needed, inspected by appropriate agency personnel.

market ← الدواء اله خمس سنوات في ال available ← عادة يكون ← Significant body of information

Validation ← التحقق من ال parameter اللي بتأثر في عملية التصنيع وقت الخلف طريقة إضافة المواد

Change in batch size

- **Level 1 of changes**
- Changes in the batch size up to and including factor of **10 times the size** of the pilot / biobatch where
  - The **equipment is of same design and principle**
  - Both manufacturer. According to the CGMP compliance.
  - **Same SOP's** followed
- Test and filing documents are same as of the level 2 of the site changes requirement.

Change in batch size

- **Level 2 changes**
- Changes in the batch size beyond the **factor of 10**
- Test documentation
  - As per level 1 + **one batch with three months accelerated stability + Case B dissolution testing.**

Manufacturing changes

↳ change in equipment.

A. Equipment

- Level 1 changes
- This consist of
  - Change **from non-automated to automated** or vice versa to move ingredients
  - Change to alternative equipment of same design and the operating principle of **the same or different capacity**
- Test and filing documentation – as per level 1 of batch size change

Manufacturing changes

- **Level 2 change**
- Change in **equipment to a different design**
- Test and filing documentation
  - As per level 3 of the site change except Case C dissolution instead of Case B.

annual report.

long term stability data

prior approval → Chemistry, dissolution

5 media dissolution study.

Ex:

Dry - granulation → slugging / Roler compacter → إذا تغيرت من طريقة لطريقة level 2

- significant body of information → one Batch accelerating study and long term stability data
- No significant body of information → 3 Batch accelerating study 3 months.

Manufacturing changes

B. Process changes → 3 levels.

- Level 1 change
  - This changes includes process changes like mixing times and operating speed within application/validation range
- Test and filing document as per level 1 of site change.

→ annual report only.

Manufacturing changes

- Level 2 change
  - This changes includes process changes like mixing times and operating speed outside the application/validation range

غيرت خارج ال range تبقى

- Test and filing documentation – as per the level 2 changes in site changes

→ accelerating test 3 months.
→ dissolution B.
→ long term stability on annual report.

Manufacturing changes

- Level 3 change → change the process of manufacturing
  - Change in the type of the process used in the manufacture of the product, such as a change in from the wet granulation to the direct compression of dry powder.
- Documentation – As per the level 3 changes of components and composition changes

. direct compression. إلى wet granulation من غيرت

1. Bioequivalance. 2. dissolution → case B. 3. accelerating 3 months data.

4. Long term stability data annualy.

SUPAC-MR

- Components and composition-Nonrelease controlling excipient
  - Focuses on changes to nonrelease controlling excipients.
  - Changes in components or composition that have the effect of adding a new excipient or deleting an excipient are defined at level 3.

Level 1 changes

- Test documentation
  - Chemistry documentation
  - Application/compendial product release requirement
  - Stability: First production batch-Long term stability
- data Dissolution documentation: None
- Bioequivalence documentation: None
- Filing documentation
  - Annual report- all information including long term stability data

Level 2 changes

- **Test documentation**
  - Chemistry documentation
  - Application/compendial product release requirements and updated executed batch records.
  - Stability: One batch with three month accelerated stability data reported in prior approval supplement and long term stability data of first production batch reported in annual report.
  - Dissolution documentation
  - Extended release
  - Multipoint dissolution profile in 0.1N HCl and USP buffer media at pH 4.5 and 6.8 for the changed drug product and the bio batch or marketed batch (unchanged drug product).

Level 2 changes

- **Bioequivalence documentation:** None
- **Filing documentation**
  - Prior approval supplement (accelerated stability data) annual report (long term stability

Level 3 changes

- **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.

Level 3 changes

- **Bioequivalence documentation**
  - A single dose bioequivalence study.
  - The bioequivalence study may be waived in presence of an established in vitro/in vivo correlation.
- **Filing documentation**
  - Same as level 2 changes.

Site changes

- It 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 cGMP inspection.
- A stand alone packaging operations site change and laboratory changes, may be submitted as a Changes Being Effected Supplement

Manufacturing equipments changes

- Manufacturing changes may involve the equipment used in the manufacturing process (critical manufacturing variable)
- If 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.

Manufacturing equipments changes

- **Level 1 changes**
  - It 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.
- **Test documentation and filing documentation**
  - remains same as non release controlling excipient.

Manufacturing equipments changes

- **Level 2 changes**
  - Change in equipment to a different design and different operating principles.
- **Test documentation and filing documentation**
  - remains same as non release controlling excipient.

Manufacturing process

- Changes involve the manufacturing process itself.
- Validation studies should be conducted in case of process changes.
- 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.

Manufacturing process

- **Test documentation**
- Chemistry documentation
  - None beyond application/compendial product release requirements.
  - Notification of the change and submission of the updated executed batch records.
- **Other documentation** remains same as non release controlling

Manufacturing process

- **Level 2changes**
- This category includes process changes involving adjustments of equipment operating conditions such as mixing times and operating speeds outside of original approved application ranges.
- **Other documentation** remains same as non release controlling excipient

Manufacturing process

- **Level 3 changes**
- 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.
- **Other documentation** remains same as non release controlling excipient.