31 كانون ثاني
12, 7

احنا بنلش بـ pilot scale وبنكبر التصنيع لـ product
وبعد ما ناخذ الـ registration معناتها كل تغيرات بعد
الـ approved (تغير في التصنيع، تغير
مادة اولية)

Scale-Up and Post Approval Changes (SUPAC)

What is SUPAC?

في البداية بس بتحضر الدوا
وبنقل الدراسات السريرية
بنلش نغير الـ Formula
هو كان substance بعير
new drug Formula
(drug + exepient)

- In the process of developing new drug product , the batch size used in earliest clinical and stability studies are small.
- The sizes of the batch is then 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)

اول batch بتحضر عشان
الكلينيكال ودراسات
الـ Stability وبتكون
الصد وبعد نتيجة بعير
scale up

اي شيء بحصل خلال او بعد عملية الحصول على الموافقات

What is SUPAC?

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

ملحق

Rationale of SUPAC guidelines

- to speed up the processes of post approval changes of drug products

لانه اي تغيير مثلا تتوقف ماكينة او يتوقف الـ supply لحاجة معينة او يصير تغيرات

- FDA can assure their safety and effectiveness.

لانه يتم التغير على الظروف المعينة اللي تم التسجيل فيها

- lower the regulatory burden for industry.

الوضع يضل يكون اسهل بالتخفف من الـ regulation

SUPAC guidelines

These guidelines provide recommendation for post approval changes in:

- component or composition
- the site of manufacture
- the scale up of manufacture
- the manufacturing process
- the manufacturing equipment

سواء راح لصنع مختلف في نفس الدولة أو في دولة أخرى

SUPAC guidelines

The guidance defines:

من كل التغييرات واحد

- levels of change;
- recommended chemistry, manufacturing, and controls (cmc) tests for each level of change;
- *in vitro* dissolution tests and/or *in vivo* bioequivalence tests for each level of change; and

من اهم الـ tests

- documentation that should support the change.

Levels of changes

- **Level 1 changes** are those that are **unlikely** to have any detectable impact on formulation quality and performance.
- **Level 2 changes** are those that **could** have a significant impact on formulation quality and performance.
- **Level 3 changes** are those that are **likely** to have a significant impact on formulation quality and performance.

SUPAC-IR

Level 1 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
- Minor changes in excipients according to Table 1

Level	Excipients	% Change (w/w_{total}) Allowed
	Glidant: Talc; Other	+/- 1.0%; +/- 0.1%
	- Disintegrant: Starch; Other	+/- 3.0%; 1.0%
	- Binder	+/- 0.5%
	- Lubricant: Ca/Mg Strt; Other	+/- 0.25%; +/-1.0%
	- Filler	+/- 5.0%
	- Film Coat	+/- 1.0%

SUPAC-IR

LEVEL 1: 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.

Example: SUPAC-IR

Level 2 changes 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 for Level 1 change but less than or equal to the following percent ranges (which represent a two fold increase over Level 1 changes):

Level	Excipients	% Change (w/w_{total}) Allowed
II	- Glidant: Talc; Other - Disintegrant: Starch; Other - Binder - Lubricant: Ca/Mg Strt; Other - Filler - Film Coat	+/- 2.0%; +/- 0.2% +/- 6.0%; 2.0% +/- 1.0% +/- 0.5%; +/-2.0% +/- 10.0% +/- 2.0%

SUPAC-IR

LEVEL 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.

بـ level 1 طلب على ال long
لأنه التغيرات هيك unlikely

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SUPAC-IR

LEVEL 2: Test Documentation

يعتمد على طبيعة الدوا ⇐ في دوا اسمه CBS
على ال permeability
+ solubility

b. Dissolution Documentation

كله oral

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 .

stomach cond

ماله مشاكل ال bioavailbility اله تمام

تباًش ال absorption

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

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لازم اعمل dissolution test بحط ال tablet في هاد ال test
ونسحب عينات على وقت وكللهم
بدنا نراقب شو بصير

SUPAC-IR

LEVEL 2: Test Documentation

b. Dissolution Documentation

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.

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SUPAC-IR

- Dissolution profiles may be compared using the following equation that defines a similarity factor (f_2):

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

- 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.

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SUPAC-IR LEVEL 2: Test Documentation

LEVEL 2: Test Documentation

c. ***In Vivo Bioequivalence Documentation***

human Study

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

اذا كانت الوضع بعد عملية الdissolution
not fix A,B,C بكونه في مشاكل وما
بيتفقوا بالdissolution بيروحوا على level 3

SUPAC-IR

Level 3 changes 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 for Level 2 => عرفناه A,B حسب الـ solubility
- Changes in the excipient ranges of low solubility, low permeability drugs beyond those listed for Level 1
- Changes in the excipient ranges of all drugs beyond those listed for Level 2.

في حالة D يكون low, صاوهون المشكلة الدوا ويلزم الدوا يندرس على human

(1) narrow therapeutic drug exepient
(2) other drug
(3+4) low, low

SUPAC-IR

Level 3 : Test 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.

level 3 طبعهم مع بعض

Significant body of information not available:

- Up to three batches with three months accelerated stability data reported insupplement; one batch on long-term stability data reported in annual report.

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SUPAC-IR

Level 3 : Test Documentation

Dissolution Documentation ⇒ مهم جدا

low perminable / high soluble

Case B dissolution profile as described for level 2.

In Vivo Bioequivalence Documentation

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

المطلوب هي bioequivalence human study تقابلها ال in vitro dissolution

profile للحصول حسب level3 ال human كاملة تنقل وتتقدم

بسمحوا بإتيانه اسمه waiving (تستغنى) عن ال human study

بشرط نعمل دراسة dissolution study ** احتفاظها IV.IVC

لانه دراسة ال human مكلفة فيها مخاطر بدها اجهزة حديثة

فالقوانين بتساعدهم شوي

يعني يعكس شو بصير بال human

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Table 1

Level	Excipients	% Change (w/w_{total}) Allowed
I	- Glidant: Talc; Other - Disintegrant: Starch; Other - Binder - Lubricant: Ca/Mg Strt; Other - Filler - Film Coat	+/- 1.0%; +/- 0.1% +/- 3.0%; 1.0% +/- 0.5% +/- 0.25%; +/-1.0% +/- 5.0% +/- 1.0%
II	- Glidant: Talc; Other - Disintegrant: Starch; Other - Binder - Lubricant: Ca/Mg Strt; Other - Filler - Film Coat	+/- 2.0%; +/- 0.2% +/- 6.0%; 2.0% +/- 1.0% +/- 0.5%; +/-2.0% +/- 10.0% +/- 2.0%
III	- Higher than SUPAC-IR Level 2 Excipient ranges	

LEVEL 1

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

Excipient		Percent excipient (W/w) out of total target dosage form weight
Filler		±5
Disintegrant	Starch	±3
	Other	±1
Binder		±0.5
Lubricant	Calcium or Magnesium Stearate	±0.25
	Other	±1
Glidant	Talc	±1
	Other	±0.1
Film Coat		±1

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SUPAC-IR

Level 3 : Test Documentation

Filing Documentation

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

prior approval تعني ملحق لـ

٠٩/٠٥/١٤٤٤

Component and composition changes

- Focus on the changes in amount of excipients in the drug product
- Not focus on change in the amount of the drug substance.