

Scientific and Regulatory Challenges in Seeking Post-Marketing Changes (Non-sterile products)

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Synopsis

- **Policy & guidelines for Post-marketing changes**
 - Types of changes
 - General requirements
- **Common deficiencies**
- **Suggested solutions**



Four Levels

Impact of change on quality & performance

Level 1 – Likely to have significant impact (SNDS) .



Level 2 – Could have significant impact.



Levels 3 & 4 – Unlikely to have significant impact.



Level 1 - Supplemental New Drug Submission (SNDS/SANDS)

Notice of Compliance required for implementing change. The SNDS:

- 🔔 may be due to change in dosage form or product strength.
- 🔔 requires clinical or bioequivalence data to support significant change(s) in:
 - formulation (all products)
 - manufacturing method (all products)
 - process and equipment (all products)
 - change in specification to remove the sterility test or replace sterility test with process parametric release (sterile products)



Level 3 : Notice of Change

- 🔔 Supporting data need not be submitted, but the data must be available at the Sponsor's premises. Examples:
- 🔔 **Analytical methods:** with increased precision, accuracy, sensitivity etc.
- 🔔 **Specifications:** addition of a test or tightening of existing test limits.
- 🔔 **Expiry period** (subject to the Policy on Extension of Expiration Dates): for extending the expiration period of a drug product when the original expiration period is 2 years or more. Full long term data on 3 commercial scale batches.



Level 4 change

- 🔔 Changes made without notification but the list of changes should be maintained by the Sponsor.
- 🔔 Example: Change in specification to comply with the corresponding change in compendia such as USP or Ph. Eur.



Level 2: Notifiable Change

(emphasis on orally delivered products)



Level 2 - Notifiable Change

- 🔔 Extent, details and scientific justification of information same as in SNDS.
- 🔔 Must be filed & approved prior to making the change.
- 🔔 Default period of 90 days: Unless a written objection is received from the Branch within 90 days, the Sponsor may proceed with the change.
- 🔔 Level 2 changes generally fall in the following categories: Drug Substance, Drug Product, Excipients, and Packaging.



Level 2 - Notifiable Change (Cont'd)

I. **Drug substance:** Change in

- manufacturer/supplier
- method of synthesis/manufacture
- specification (impurities, particle size etc.)

II. **Excipient:**

- change in specification that could impact quality

E.g., change in polymer mol. wt., viscosity etc.



Level 2 - Notifiable Change (Cont'd)

III. Drug product: Change in

- manufacturing site.
- manufacturing method and equipment.
- specifications: in-process/release/shelf life.
- shelf life (outside extension policy) and storage condition.
- container size (for sterile products)



Level 2 - Notifiable Change (Cont'd)

IV. Packaging:

- Additional/alternative packaging site
- Change in specifications/composition of packaging material which is either in direct contact with the drug product or help to ensure the stability, sterility or delivery of the drug product.



Recommended documentation details

- 🔔 Electronic format & hard copy
- 🔔 **Accurate** and **complete** description of **ALL** proposed changes (Covering Letter/ Brief Summary/QOS-CE).
- 🔔 **Summary** with supporting scientific rationale justifying the proposed change.
- 🔔 **List of all changes:** previously submitted and annual notifications.
- 🔔 **Index** the list of all documents/attachments.
- 🔔 **Nature of change:** replacement *vs* additional/alternate



Documentation details (Cont'd)

- **Comparative data:** One of the best ways to present data of the proposed change is by comparison in a side by side table. The current and/or initial clinical/bio lot should be taken as the **reference**.
 - **E.g., change in drug substance synthesis should include**
 - ❑ Current & proposed synthetic route
 - ❑ Comparative impurities & solvents (based on actual data)
 - ❑ Comparative particle size analysis if applicable
 - ❑ Comparative specifications
 - ❑ Stability test results to support retest period



Documentation details (Cont'd)

- **E.g., change in drug product process should include comparison of:**
 - manufacturing equipment and operating parameters (type, size & make)
 - dissolution profiles (in multiple pH in certain cases) and f2 determination where applicable.
 - specifications
 - stability results



Documentation details (Cont'd)

- **Data evaluation and conclusion**
- **Copies of current and proposed manufacturing batch records**
- 🔔 **Specifications (in-process, release & stability)**
- **GMP compliance**
- **Stability test results (as per ICH conditions)**



Documentation details (Cont'd)

➤ **Commitments**

- Validation of first three commercial lots
- Stability of first two commercial lots

➤ **Process validation protocol**

- Product specific process details
- Sampling details
- Acceptance criteria

 **Revised Product Monograph** (3 pristine copies, electronic copy, certification)

 **Revised CPID-CE** (electronic copy)



Certificate of analysis

- 🔔 Copies of the current and proposed drug substance or drug product test results (changes should be highlighted)
- 🔔 Revision/ approval dates/ code numbers
- 🔔 Analytical method validation where necessary



Why post-marketing changes are made?

- 🔔 For improving process, quality, efficiency, or cost
 - Desirable - both Sponsor & patients benefit.
- 🔔 Due to business reasons (mergers, consolidation etc.)
 - Generally unavoidable but it is hoped the change will benefit all.
- 🔔 Due to poor planning at the product development stage, changes are proposed soon after getting approval.
 - Not desirable – evaluation of NC is more challenging due to lack of ‘historical’ data on the marketed product.




Important point to remember

Certain NDS or ANDS are approved with *in vitro* tests that are NOT most suitable: E.g.,

- Dissolution test is non-discriminating.
 - Limited process challenge studies done during scale-up.
- Such a test *might have been accepted* at the time of initial submission either due to physicochemical limitations of drug substance, or due to lack of scientific understanding at that time. However, such submissions would have had supporting clinical/bio studies.



Important point...

 The same *in vitro* test (e.g., a non-discriminating dissolution test) can NOT be used to justify a major post-marketing change when it is not supported by accompanying clinical/bio data. This is especially true for drug products with poorly soluble drugs compounded with insufficient developmental work at the initial (NDS/ANDS) stage.



Examples of deficiencies (solid orals)

1. **No rationale is provided for the proposed the change which is significant in nature. E.g., change in granulation process from low to high shear.**
 - As a result the ‘Worst case’ scenario is assumed, and the review takes more time.
 - ✓ **Solution:** Provide a scientific rationale for making the change. This will help the Branch to look in the right direction, resulting in speedy evaluation of the submissions.



Examples of deficiencies (cont'd)

2. **Change in site or alternate mfg site not supported by transportation studies: E.g.,** transportation of
- granules (for compression) to a different site
 - core tablets (before coating or for packaging) to a different site.
 - The usual stability of drug product in marketed container (accelerated & long term) is not sufficient to support a site change involving transportation of unfinished product.
 - The one-time study should include: packaging & transportation details, complete analysis before and after transportation, holding time study, and type of device used for monitoring temperature & humidity.



Examples of deficiencies (cont'd)

3. **Change in process and/or equipment without providing supporting data. E.g., change from:**
- **low to high shear granulation**
 - **oscillating granulator to Fitz mill**
 - **tray drying to FBD drying**
 - **Such changes may result in a change in the granule density, and granule particle size distribution, ultimately leading to different dissolution profile.**
 - **Such changes are very difficult to evaluate when the dissolution method is not discriminatory in nature.**



Examples of deficiencies (cont'd)

4. **Improper use of dissolution tests to support a NC**
 - Many submissions have a one-time-point dissolution in a medium containing a solubilizer (e.g., Q 75%, 20 min, 0.1 N HCl with 0.5% SLS). Often the method is not discriminatory.
 - Multiple pH study not done when required.
 - f_2 values not properly calculated
 - E.g., More than one point after 85% release used for calculation; fewer samples used (n=6, instead of 12).
 - Graphical profiles not included



Common deficiencies

5. Other common deficiencies are:

- I. All previous changes not listed/summarised.
- II. No information about GMP compliance of the proposed new site.
- III. CofA from new drug substance supplier is incomplete/does not conform with approved specification (e.g., particle size, impurity levels etc.).
- IV. Change in retest period not justified
- V. Comparison of equipment and process not provided.



Common deficiencies (Cont'd)

- VI. Adequate stability results not provided**
- VII. In-process test criteria changed without justification (e.g., hardness, pH, viscosity)**
- VIII. CPID-CE does not represent the approved drug substance, product and packaging.**
- IX. Stability and validation commitments not made.**
- X. Validation protocol lacks product specific details.**



Conclusion

Formulation development, process development, scale-up, manufacturing and analytical method development require a very systematic planning, to build robustness. Products made this way can withstand post-marketed changes more predictably. Achieving this goal would be further facilitated by the use of tools such as PAT (Process analytical testing).



Thank you!
Merci !



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