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Post-NOC Changes – Quality Guidance Overview and Update

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The secret of change is to focus all of your energy, not on fighting the old but on building the new - Socrates

Outline

- Historical perspective of post-NOC change.
- Guiding principles in developing one of the most detailed and complex guidance documents.
- Some salient points and recent updates.
- Observations from submissions and HRAs.
- ICH Q12 – Product lifecycle management.

History of Post-approval changes

- Changes to Marketed New Drug Products – 1994 with a 90-day default period :
  - Huge number of submissions (about 30-50 per month).
  - Lack of detailed guidance.
  - Many submissions were big (SNDS/SANDS).
  - No provision for cost recovery.

History of Post-approval changes

- Post-NOC Changes: Revised and detailed Quality document effective September 2009 – 8 appendices.
  - Human pharmaceuticals section – received positive feedbacks from stake holders on the level of details.
  - Default period eliminated; but the submission back log was not reduced significantly.

History of Post-approval changes

- Revision - September 2011 - Separate Appendix I for Human Pharmaceuticals.
  - Level II changes were eliminated. Only two categories of changes were allowed – Supplements (level I) and Annual Notifications - AN (level III).
  - Elimination of NC backlog helped the **industry to take more responsibility** to manage their product lifecycle and allowed Health Canada to better utilise the available resources.

What's has changed?

- 39 changes - 6 changes require filing of Annual Notification (AN) only.
- Change #14 – addition of a dosage form/strength requires filing of supplement (i.e. AN not permitted)
- 32 changes can potentially be filed as ANs **if** conditions for AN are met (**Notable exceptions:** most changes related to high risk products - Modified Release /Sterile products and design space are considered level I).

Guiding Principles

- **Scientific knowledge provides opportunity to self-assess risks that could provide *regulatory relief based on.***
  - In-depth knowledge on manufacturing process for Drug substance (DS) and Drug product (DP).
  - Experience in scale-up, process validation and manufacturing of DS and DP commercial batches.
- **Challenge**: Knowledge sharing/management with contract service providers is often inadequate – ultimately it is the Sponsor's (distributor/importer) responsibility to ensure acceptable quality is maintained in drug product lots!

Guiding Principles
Appendix I (Human Pharmaceuticals)

- Sponsors have the opportunity to **assign risk** and the flexibility to **manage *certain* changes** without seeking regulatory approval prior to implementation. This places **greater responsibility on Sponsors**.
- **Caution:** Post-NOC change guidance **should not** be used to circumvent pre-approval requirements as there would be insufficient product knowledge to make meaningful risk assessment.

Additional Considerations

- Regulatory compliance
- Legal considerations
- GMP for drug substance manufacturing site (now a regulatory requirement).
- Potential for product recall if a change is not implemented properly.
- Making post-approval changes is not simply a policy-based exercise. It requires scientific assessment of the risk to be made before making the change.

Risk Assessment – points to be noted

- Supporting data should be generated (and available) **prior** to implementation of annual notification.
- Impact of multiple changes on filing category should be assessed (e.g. change in specification and shelf life) not only from a policy but **from a risk/scientific perspective**. This means the Sponsor should involve their scientific/technical staff in the decision making process.

Risk Assessment – points to be noted

- Supplement is the default filing category when objective assessment of risk is not possible without prior review of data.
- Ability to submit a request for biowaiver doesn't imply it would be accepted; depending on the data/justification and level of risk, additional study (including a BE study) may be requested.

Risk Assessment – points to be noted

- The Sponsor is responsible to ensure the drug substance & product meet the expected quality at all times during the lifecycle of the product.
- The **approved specification** is applicable only for the approved formulation, manufacturing process, control strategy and container closure system. If there are significant changes to these elements the existing specification (for DS and DP) is no longer valid.

Risk Assessment – points to be noted

- Marketing unapproved product with significant changes made inappropriately could be a regulatory violation: Examples
  - qualitative change in excipient.
  - using unapproved manufacturing process (e.g., change from terminal sterilization to aseptic process or change from granulation to direct compression).
- Such products could be recalled and subject to additional compliance action.

Change #23
Replacement or addition of a manufacturing site for DP

- Sterile and Modified Release (MR) products – high risk categories - require filing of supplement.
- Immediate Release (IR) products – may be filed as AN if the conditions are fulfilled (e.g., GMP compliant site, successful validation at existing and proposed sites **prior** to implementation).
- Sites for packaging, testing and storage and distribution - may be filed as AN if the specified conditions are fulfilled.

Change #23
Replacement or addition of a manufacturing site for DP

- **Assumption:** It is assumed the Sponsor would have gained sufficient knowledge on the IR product and process robustness at the **existing approved site** so that site transfer would only be a tech-transfer and would not involve complex scale-up and process optimization exercise.
- The Sponsor is **not** expected to use this change as part of the lifecycle management (business) plan prior to launching the product from the initially approved site.

Changes 24 and 25

Change in **batch size** and **manufacturing process** of DP

- Batch size:
  - Increase beyond 10 times for MR: Supplement and AN for <10 times.
  - IR dosage forms: AN with conditions & supporting data.
  - Batch size change should NOT be due to batch failure.
- Manufacturing Process: If process needs to be changed due to unexpected events (e.g., stability failure /scale-up)
  - Supplement would be required.

Change # 31
Change in specification & acceptance criteria for DP

- Supplement is required for replacing sterility test with Process parametric release (PPR).
- Deletion, addition, replacement of test could potentially be filed as ANs if conditions are met.
- Relaxation of acceptance criteria could potentially be filed as AN if conditions are satisfied.
- Tightening of acceptance criteria is considered an AN.

Change # 31
Change in specification & acceptance criteria for DP

- **Relaxation** of an acceptance criteria

– **Principal Conditions:**

- Change is not due to unexpected events during manufacture or due to stability concerns.
- No change in assay limits and no change in the impurity profile that could impact safety.
- Change does not affect drug release of MR products.
- Change does not concern sterility testing.
- Relaxed criterion is in accordance with schedule B monograph.

Change # 31

Change in specification & acceptance criteria for DP

- Relaxation of an acceptance criteria (Cont'd)
  - Principal Supporting Data Requirements:
    - Updated specification with justification for the change.
    - If a Schedule B standard is claimed but in-house analytical method used – equivalency report is required.
    - Test results from at least one batch of pilot scale.

Change #37

Change in the shelf life of the drug product

- Extension and Reduction can be filed as **AN with conditions**

- **Principal Conditions:**

- No change in container-closure in direct contact with product.

- Approved shelf-life is <u>less than</u> 24 months: no significant trends in data for potency and purity (**<u>no extrapolation</u>**) – could be extended up to 24 M (unless specified otherwise by TPD).

Change #37

Change in the shelf life of the drug product

- Approved shelf-life is at least 24 months, full long term data covering proposed revised shelf-life available on **3 commercial scale** batches.
- No significant changes (as per ICH Q1A) observed in stability data.
- Reduction in shelf-life due to stability concern could be AN provided Sponsor's assessment has determined that there is no impact on patient safety.

Recent updates – 2015 and 2016

Appendix 1: Quality Post-NOC Changes (Human Pharmaceuticals)

Additional Clarification [Excerpt]

One of the key assumptions is that the company would **gain significant** amount of experience and knowledge on the **product during its commercial manufacturing** in the post-approval part of the lifecycle. This experience and knowledge would enable the company to perform the required risk assessment on the post-NOC change under consideration to evaluate the potential impact on quality, safety and efficacy and determine if the proposed change would be Level I or III.

However, if the company needs to make the change before gaining significant experience and knowledge (e.g., before making commercial batches) the company should submit a supplement.

Recent updates – 2015 and 2016

Change #	Description	Reason/explanation
2	**API manufacturing site**	Discussed separately
4	**API manufacturing process**	Added *starting material* along with intermediate (4 a) and deleted from (4 b).
6, 7 & 30	**Standard claim**	Change from *professed* to *house* standard was left out in earlier version and is included in the update.
18	**Change in product marking**	Change in product marking should **not** impact **safety**. This was clarified due to safety issues identified in a HRA that resulted in product recall.
23	**Addition of DP site** The word *multi-media* added in supporting data	This is only a clarification and is already implied in Appendix 5

Recent updates – 2015 and 2016 (cont'd)

Change #	Description	Reason/explanation
24	**Change in Batch size: downscaling**	Supporting data for downscaling batch size (same as for increasing batch size) for consistency as the risks/challenges are similar.
25	**Change in the drug product manufacturing process**	Additional clarification to have *in vivo* (BE) data or IVIVC to support significant change to manufacturing process of **MR** products. Companies were misinterpreting *biowaiver* for MR products and were providing only *in vitro* data which is not sufficient.

Risks associated with Changes 2 and 4 in DS

- It is Sponsor’s responsibility to ensure the controls on raw material quality are adequate.
- APIs are often outsourced and the communication between Sponsor and DS supplier (DMF holder) is not frequent and/or not adequate.
- GMP and other quality deficiencies are linked to safety issues and could result in product recall.
- Changes in starting material and intermediate could result in new impurities that are not evaluated and controlled.

Post-NOC Change Update on #2

2. **Replacement or addition of a manufacturing site and/or manufacturer involving**:

- No Level I changes in the drug substance synthesis (including starting material, intermediates and controls), analytical methods, specifications (e.g. no change in the polymorphic form ……..for insoluble drug substances as defined by dose-solubility ratio in physiological pH 1.2-6.8 - see Appendix 5) and impurity profile that impacts safety of the drug substance) .
- The change of source is supported by a valid Certificate of Suitability (**CEP**) issued by the EDQM and a DMF/ ASMF)

OR

Post-NOC Change Update on #2 - API manufacturing site

OR

- The proposed **new site** is a subsidiary **of the approved manufacturer**, under the same corporate structure / quality management or is a contract manufacturer working for the **approved manufacturer** (to manufacture SM or Intermediate or API that has already approved y HC) under a signed agreement. [There is NO new information that HC has NOT reviewed and *approved*]
- If there is a new (contract) manufacturer supplying SM or Intermediate whose synthetic process (or DMF) has not been reviewed by HC, it would require filing a supplement.

Post-NOC Change Update on #2 - API manufacturing site

OR (Cont'd)

- The new/proposed API manufacturing facility has a Drug Establishment Licence (DEL) for API fabrication, or was successfully added to Drug Establishment Licence of the Canadian importer. (DEL not required for SM or Intermediate but the site has to be GMP compliant)

- For the proposed site that fulfils above conditions **technology transfer** and **process validation** studies should be **successfully completed** for **commercial batches**.

Examples of Observations
Regulatory non-compliance

Approved specification is applicable only for the **approved** formulation, manufacturing process, control strategy and container closure system.

- Marketing drug product with unapproved formulation:
  - Qualitatively different (excipient) – e.g., new disintegrant added.
  - Quantitatively different (amount of excipient exceeds Appendix 6) and risk evaluation/justification is inadequate.

Examples of Observations
Regulatory non-compliance

- Marketing drug product manufactured using a process that is significantly different from the approved manufacturing process.
- Using unapproved API source/supplier (does not meet the conditions described in Change #2 and has not been approved by HC).
- Using an expiry period (does not meet the conditions described in Change # 37) that has not been reviewed by HC.

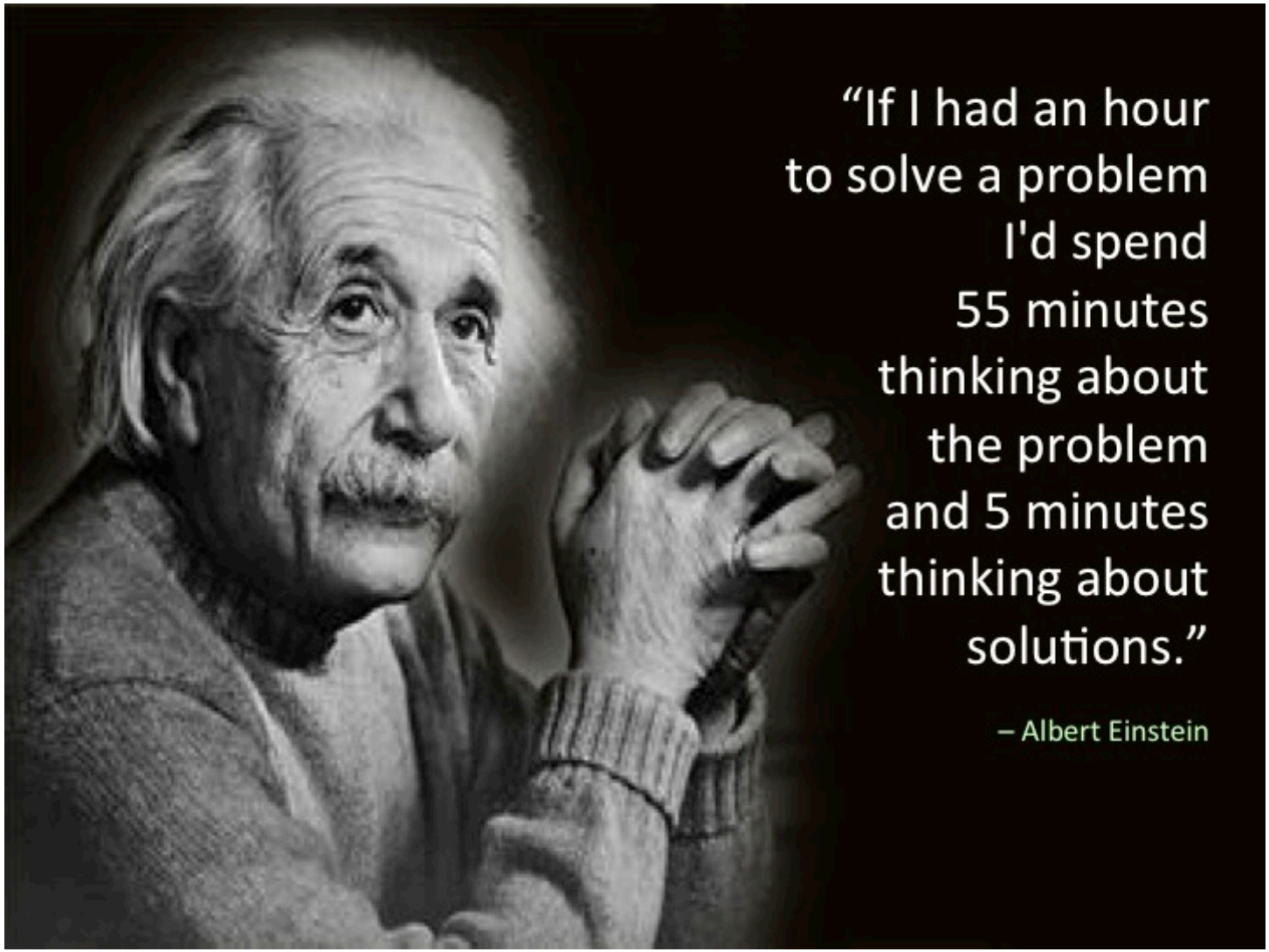
Examples of Observations
Regulatory non-compliance

- **Changing tablet marking** without evaluating the safety issues (causing confusion in dose selection and medication error).
- Observations:
  - The **justification** for the above changes are not based on scientific principles and often *in-vitro* QC tests are used to justify the change.
  - Often the medical risk assessment and justification do not consider the impact of the change on bioavailability of the proposed change on patients.

ICH Q12 – Product lifecycle management

- Complex document, expected to reach Step 1 in 2017.
- Industry has adequate representation (e.g., innovative, generic, OTC, API groups) in the expert working group.
- Post-NOC change guidance is expected to be modified to reflect the harmonised ICH Q12 guidance.

Questions ??


"If I had an hour
to solve a problem
I'd spend
55 minutes
thinking about
the problem
and 5 minutes
thinking about
solutions."
– Albert Einstein

Thank you!

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