Experience with Health Canada's Approach for Post-Approval Changes

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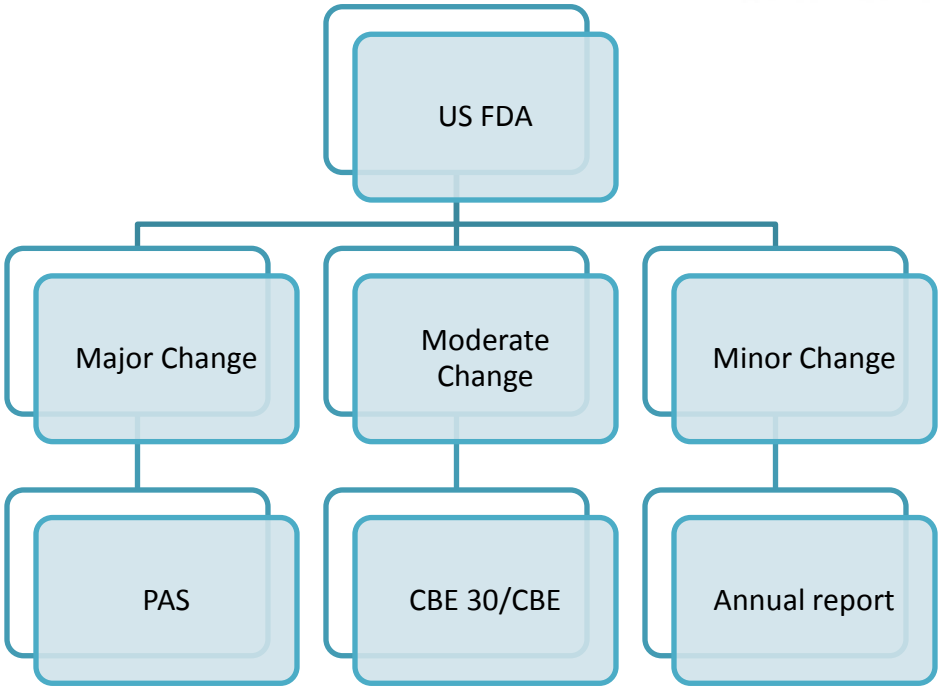
Important Quotes to consider

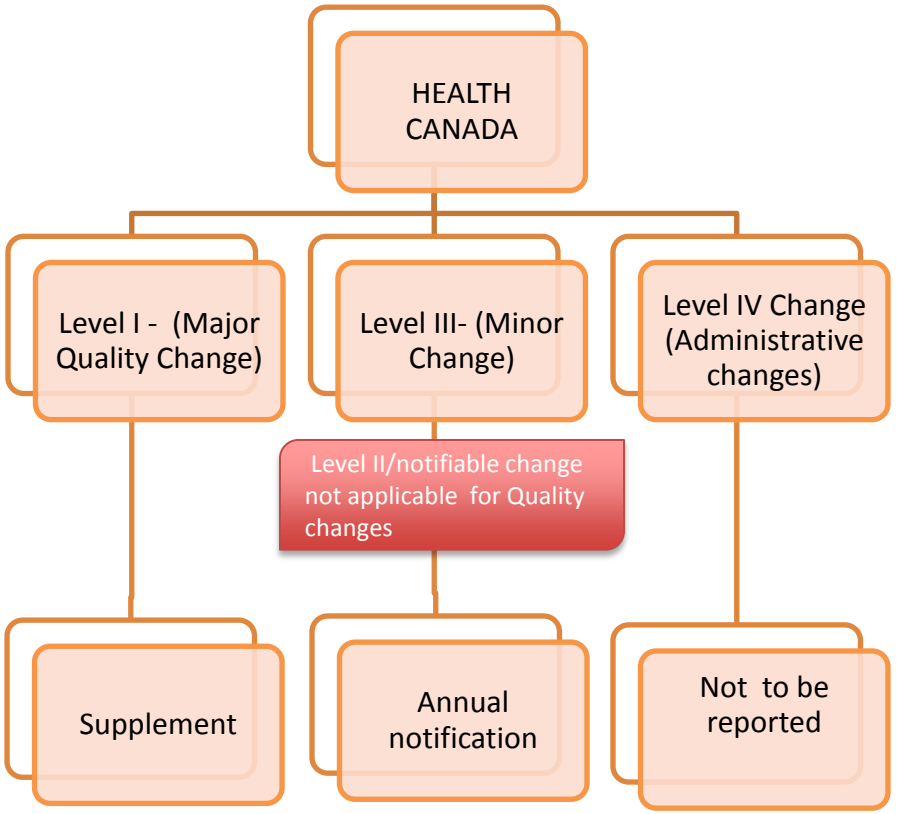
- **Dr. Janet Woodcock** on desired state:
  - "A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high-quality drug products without extensive regulatory oversight."
    - Science-based decisions
    - Risk-based approach
    - Regulatory flexibility
- **Dr Lawrence Yu on benefits of QBR System**
  - assure product quality through design and performance-based specifications,
  - facilitate continuous improvement and **reduce CMC supplements through risk assessment,**
  - enhance the quality of reviews through standardized review questions, and
  - reduce CMC review time when applicants submit a QOS that addresses the QbR questions

Experience with Health Canada's Approach for Post-Approval Changes-Implemented Oct 2013

- ✓ Comparison of Reporting Categories (FDA and Health Canada)
- ✓ Health Canada PNOC (Post-Notice of Compliance) guidance- Underlying Principle
- ✓ Health Canada PNOC Guidance- How the Level II change was Eliminated
- ✓ Discussion on the specific changes and PNOC guidance recommendation
- ✓ Supplements- Opportunities to Explore and Next Steps

Post approval Changes- US FDA/Health Canada





US-FDA Reporting categories

Prior approval- Supplement major changes

Substantial potential to adversely affect the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product.

Product made with change not be distributed until approval

CBE or CBE-30 - moderate changes

Moderate potential

Product distribution upon receipt of application to FDA (CBE) or 30 days after receipt of application to FDA, if acceptable (CBE-30)

Annual report - minor changes

Minimum potential

Annual reportable and immediate product distribution permitted

Health Canada Reporting categories*

Level I-Supplements

(Major Quality Changes

Substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product

Level II Notifiable Changes
Moderate Quality Changes

Not applicable

(For quality changes with human Pharmaceuticals , applicable for safety changes)

Level III- Annual Notification
Minor Quality Changes

Changes with Minimum potential – to be reported in an annual notification

Level IV Changes - Record of Changes

Minor administrative changes- not to be reported to the Agency

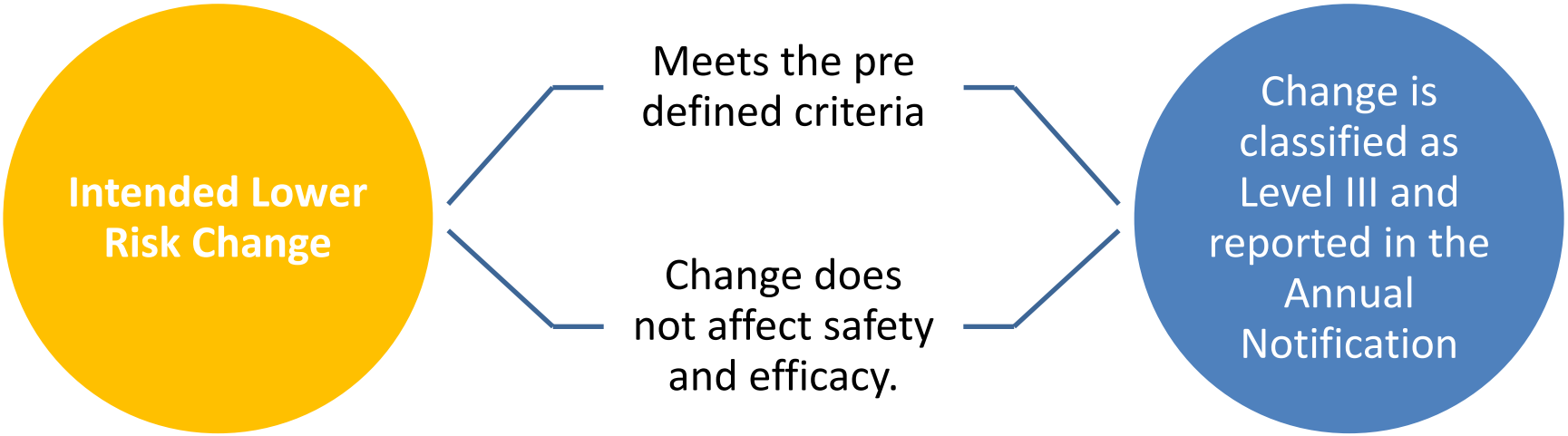
* Post NOC Changes—Quality Guidance, implemented October 2011 eliminates level II (Notifiable Change) and moves higher-risk submissions to level I while moving lower-risk changes to level III. The intent of this revision was to provide greater clarity for filing requirements of supplements without affecting safety and efficacy.

Health Canada PNOC Guidance - Underlying Principle**

- Development of a new, more comprehensive guidance document that:
  - is more consistent with modern principles of risk management
  - Facilitates international harmonization
  - replaces out-dated policies and guidances
  - is better supported by the *Food and Drug Regulations*
  - increases the transparency and consistency of the review process
  - incorporates “design space” concept from ICH Q8

**Post-Notice of Compliance (NOC) Changes Presentation to CAPRA

Health Canada PNOC Guidance- How was the Level II change Eliminated



Post approval- Manufacturing site changes

Change Description (drug substance and drug product)	Health Canada	US FDA
Replacement or addition of a manufacturing site and/or manufacturer involving production of the intermediate or drug substance	***Annual notification** ✓No Level I changes in the drug substance specifications (e.g. no change in the polymorphic form) ✓The change does not require the filing of a new DMF ✓No change in the route of synthesis ✓No new impurity above 0.10%, no change in the approved total impurity limit and residual solvents within ICH limits	**CBE-30/PAS**
Change to a different site for manufacturing or processing or packaging or testing of any drug product.	***Annual notification** ✓The drug product is for immediate release. ✓The proposed facility would need GMP rating or included in the Establishment License ✓No Level 1 change in the composition, manufacturing process and drug product specifications or container/closure system ✓Three consecutive commercial scale batches have been successfully validated at new site	**CBE-30**
A move to a different manufacturing site for the manufacture or processing of the final intermediate	***Annual notification** ✓No change in the route of synthesis ✓No new impurity above 0.10%, no change in the approved total impurity limit and residual solvents within ICH limits	**CBE**

* Examples of **conditions to be fulfilled-** Post notice of Compliance Changes Quality Document Oct 2013

Post approval- Manufacturing process changes

APOTEX

Change Description	Health Canada	US FDA
For drug substances, any change in process and/or process parameters	***Annual notification** ✓No change in the physical state of the drug substance(Polymorphic form) ✓No Level I change in the drug substance specifications, no change in particle size distribution ✓Same intermediates, no change in route of synthesis ✓No new impurity above 0.10%, no change in the approved total impurity limit and residual solvent limits within ICH ✓The change does not affect sterilization process for sterile products	**CBE-30/PAS**
For drug products, any change in the process, process parameters, and/or equipment.	***Annual notification** ✓The new process has same principle. ✓Changes to equipment, operating procedures and process controls that are minor/non-critical ✓The change is not the result of unexpected events ✓Three consecutive commercial scale batches have been successfully validated ✓The change is minor and does not affect the performance characteristics of a modified release product ✓Change does not affect sterility for a sterile product	**CBE-30/PAS**

* Examples of **conditions to be fulfilled**- Post notice of Compliance Changes Quality Document Oct 2013

Post approval- Specification changes

Change Description	Health Canada	US FDA
Deleting a test has been demonstrated to be redundant and does not impact the safety or overall quality of the product.(Eg; removal of an organic volatile solvent test after atleast 10 commercial scale batches meet acceptance criteria)	***Annual notification** ✓The change is not necessitated by unexpected events ✓No change in the polymorphic form ✓No change in impurity profile. ✓Change does not concern sterility testing ✓Does not affect the performance characteristics of a modified release.	**CBE-30/PAS**
Relaxing an acceptance criterion or deleting a test to comply with an official compendium that is consistent with FDA statutory and regulatory requirements .	***Annual notification** ✓In accordance with Schedule B monograph. ✓The change is not necessitated by unexpected events ✓No change in impurity profile and assay limits. ✓Does not affect the performance characteristics of a modified release product and does not concern sterility testing	**CBE-30**

*Examples of **conditions to be fulfilled-** Post notice of Compliance Changes Quality Document Oct 2013

Post approval-Analytical Procedure changes

Change Description	Health Canada	US FDA
Establishing a new regulatory analytical procedure including designation of an alternative analytical procedure as a regulatory procedure.	***Annual notification** ✓No change in the approved acceptance criteria other than permitted by Schedule B monograph ✓Same analytical technique or principle ✓No new impurities are detected. ✓equivalent to the approved analytical procedure. ✓does not concern a novel, non-standard technique or does not concern sterility testing ✓does not impact the dissolution test condition for a modified release.	CBE 30/PAS
Change from a House analytical procedure to a Schedule B/Compendial monograph analytical procedure or a change from an approved compendial analytical procedure to a harmonized compendial procedure.	***Annual notification** ✓No change in the approved acceptance criteria other than permitted by Schedule B/Compendial monograph ✓Results to demonstrate equivalency between methods.	CBE-30/ CBE 0
* Examples of **conditions to be fulfilled**- Post notice of Compliance Changes Quality Document Oct 2013		

Post approval- in-process controls changes

Change Description	Health Canada	US FDA
Deleting an analytical procedure that has been demonstrated to be redundant with respect to the remaining analytical procedures (e.g., color, hardness), and does not pertain to a critical quality attribute of the product (e.g., blend uniformity, weight variation).	***Annual notification** ✓ No unexpected events triggering the change ✓ does not affect the sterilization parameters	**CBE-0/CBE-30**

Post approval- drug product description changes

Change description	Health Canada	US FDA
Change in fill weight/volume with no change in container /closure	***Annual notification** ✓No change in the qualitative and quantitative composition and mean mass or fill weight ✓The change does not affect the performance characteristics (e.g., release rate) of a drug product	**PAS/CBE**

*Examples of **conditions to be fulfilled-** Post notice of Compliance Changes Quality Document Oct 2013

Supplements- Opportunities to Explore

- There are quick wins that can be accomplished by reviewing the Health Canada Model
- How can industry and agency work together to reduce the number of submissions to a reasonable level ?
- Explore the enhanced use of comparability protocols to seek agency agreement on the reporting category and the corresponding documentation required.
- Explore options to reduce post approval burden based on the body of data and development work in the original submission (i.e. extend the QbD ethos and objective to the lifecycle of the product, where appropriate)

Supplements- Next Steps

Agency and Industry to consider further discussions

- On Risk based assessment of change that could potentially result in downgrading the supplement category
- On the use of comparability protocols to seek upfront consensus with the agency on reporting category and the documentation to support change.
- To determine how the use of Quality Metrics can assist in seeking post approval relief as outlined in Industry position paper on Quality Metrics

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