March 2010
CAPRA Symposium

Overview of the post-NOC changes quality guidance document - Biologics

Hugo Hamel, Senior Biologist/Evaluator, BGTD
Dr. Harold Rode, Rode Biologics Consulting Inc.



Canada

Outline

- Second consultation period: Outcome
- Post-NOC Changes Quality Guidance - Biologics: Points to Note
- Annual Notification *vs* YBPR
- Appendix 3 (Biologics) – What's new
- Conclusion
- Question period




Second Consultation Period: Outcome

- Draft PNOCC guidance documents posted externally December 5, 2008 for a 45-day comment period
  - Draft Framework document
  - Draft Safety & Efficacy (S&E) document
  - Draft Quality document
- Comment period ended January 30, 2009
  - Quality document for Biologics (Appendix 3) received 301 comments




PNOCC Quality guidance document – Biologics – Points to Note

- *Conditions:*
  - All conditions must be met in order to file the change at the proposed Level of filing
  - If any of the conditions outlined for a given change are not fulfilled, the change is considered the next higher level

- *Supporting data:*
  - Detailed rationale must be provided when recommended supporting data cannot be provided




PNOCC Quality guidance document – Biologics – Points to Note

- *Applicable to DIN-Bs:*
  - In absence of guidance specific to the Quality of DIN-Bs, the principle and the examples of supporting data described for the Schedule D drugs in the guidance are considered relevant to those product
- *Level IV Changes:*
  - List of examples of Level IV changes provided
  - May be implemented by the sponsor/manufacturer without prior review by Health Canada
  - Need to be retained as part of the drug product ‘s record by either the sponsor or the manufacturer




PNOCC Quality guidance document – Biologics – Points to Note

- *Certificate of Suitability (CEP):*
  - Are not accepted to support a drug substance of biological origin
  - CEP in support of the TSE/BSE risks for biological auxiliary material/raw materials may be accepted
- *Production documents:*
  - Master and Executed Batch Records are no longer required at time of filing of post-NOC changes.
  - Must be provided within 15 days upon request
  - Extension may be requested if translation required




PNOCC Quality guidance document – Biologics – Points to Note

- *CPID and Product Monograph:*
  - If the CPID or PM is impacted by the post-NOC changes (including Level III and Level IV), an updated CPID/PM should be provided:
    - With the filing of the next post-approval submissions
    - No longer required to be submitted as part of the Annual Notification
- *Multiple changes:*
  - It is allowed to bundle these changes
  - Indicate where the changes are related
  - Describe any association between the proposed changes




Annual Notification vs YBPR: How linkage between the documents are managed?

- *Annual Notification:*
  - Level III changes submitted with the Annual Notification consist in an exhaustive list of all product-specific Level III changes implemented in the last year
  - Level III changes must be filed no later than October of each year
  - A request for supporting data may be made after the Annual Notification is filed




Annual Notification vs YBPR: How linkage between the documents are managed?

- *Yearly Biologic Product Report (YBPR):*
  - Contains information used to assess:
    - the on-going safety and quality of the products;
    - to verify the consistency of manufacturing processes;
    - to highlight any trends.
  - Level III changes submitted as part of the YBPR:
    - allows the evaluators to have a complete picture of the manufacturing process;
    - help in the evaluation of the results obtained for the drug substance and drug product;
    - used to justify either the current lot release group or a new one.




Annual Notification vs YBPR: How linkage between the documents are managed?

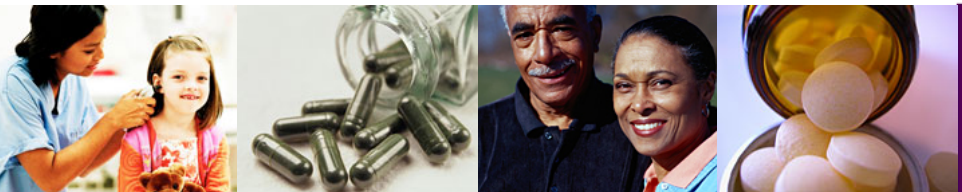
➢ *Why Level III must be submitted in YBPR?*

- While it is agreed that there may be some overlap with the Annual Notification, submission of the relevant Level III changes with the YBPRs ensure a comprehensive review of all changes implemented in the last year. The review of the relevant Level III changes integrated into the context of the YBPRs is an important part of our life cycle approach to product review.




Structure of the Quality guidance

- Introduction
- Appendix 1: post-NOC changes (Pharmaceuticals)
- Appendix 2: post-NOC changes (Veterinary Drugs)
- ***Appendix 3: post-NOC changes (Biologics)***
- Appendix 4: post-NOC changes (Schedule C drugs)
- Appendix 5: Recommendation for comparative Dissolution profile
- Appendix 6: Changes to Excipients
- Appendix 7: Examples of Level IV Changes
- Appendix 8: Glossary



Appendix 3 – What's new

3.2.S.2 Manufacture

- Replacement or addition of a manufacturing facility for the bulk drug substance, or any intermediate of the drug substance
  → ***NC (conditions 1-5)***
- Conversion of a drug substance manufacturing facility from single-product to multi-product → ***NC (condition 5)***

1. This is an addition of a manufacturing facility/suite to an approved manufacturing site **(same sponsor/company)**.
2. The process is an exact replicate of the approved process and controls.
3. The new facility/suite is under the same QA/QC oversight.
4. No changes have been made to the approved and validated cleaning and change-over procedures.
5. The proposed change does not involve additional containment requirements.




Appendix 3 – What's new (cont'd)

3.2.S.2 Manufacture

- Change to the drug substance fermentation process involving:
  a) A critical change *(e.g. new bioreactor technology)* → **Supplement**
  b) A change with moderate impact *(e.g. extension of the in vitro cell age beyond validated parameters)* → **NC (2 conditions)**
  c) A non-critical change *(e.g. addition of identical bioreactors, duplication of a fermentation train)* → **Level III (8 conditions)**

- Change to the drug substance purification process involving:
  a) A critical change → **Supplement**
  b) A change with moderate impact → **NC (2 conditions)**
  c) A non critical change → **Level III (5 conditions)**




Appendix 3 – What's new (cont'd)

3.2.S.2 Manufacture

- Change in supplier of auxiliary materials/reagents of biological origin (e.g. FBS, insulin, HSA) → **Level III (Supp. Data 1-2)**

- Change in source of auxiliary materials/reagents of biological origin (e.g. FBS, insulin, HSA) → **Level III (Supp. Data 1,3)**

Condition:

- The change is for a compendial auxiliary materials/reagents.

Supporting data:

1. Evidence that the material does not pose a potential BSE/TSE risk.
2. Description of the batches for one (1) commercial scale batch.
3. Description of the batches for three (3) commercial scale batches.




Appendix 3 – What's new (cont'd)

3.2.S.2 Manufacture

- **Changes to the cell bank/seed bank *(No changes)***
  a) New Master Cell Bank/Master Seed Bank → Supplement
  b) Generation of new WCB/WSB → Level III (3 conditions)

- **Change in <u>product-contact</u> equipment:**
  a) Replacement of equipment with <u>equivalent</u> equipment ***→ Level III***
  b) Replacement of equipment with <u>identical</u> equipment ***→ Level IV***




Appendix 3 – What's new (cont'd)

- **Change in specifications for the materials:**

a) Raw materials, starting materials → Level III (Conditions 1, 3-4)
b) Solvents, reagents, catalysts → Level III (Conditions 2-4)

Conditions:

1. The change in specifications for the materials is within the approved ranges.
2. The Grade of the materials is the same or is of higher quality
3. No change in drug substance specifications outside approved range
4. No change in the impurity profile of the DS outside the approved limits




Appendix 3 – What's new (cont'd)

- **Change to process validation protocol:**

Previous version:

- Change to a process validation protocol used during the manufacture of the DS → ***NC (1 condition)***
  1. Change to a protocol approved by BGTD (e.g. cell banks)

Current version:

- Major change to the following process validation protocols used during the manufacture of the DS → ***NC (no condition)***
  - ✓ Manufacture of cell banks, cleaning of equipment, introduction of new product into a multi-product facility




Appendix 3 – What's new (cont'd)

3.2.S.4 Control of the Drug Substance

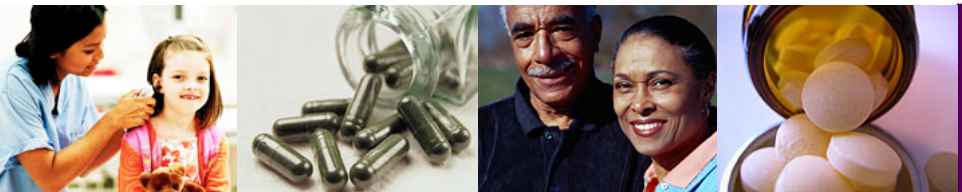
- Changes affecting the QC testing site **(release and stability)**:

Previous version: ***→ Level III (1 condition)***

- Could be filed as Level III or NC depending if the test transferred was a bioassay and the new testing site was under the same QA/QC oversight (i.e. with the same QA/QC signing authority)

Current version: ***→ NC (no condition)***

- A NC is required for the transfer of all non-pharmacopoeial assays
- Transfer of pharmacopoeial assays can be filed as Level III (except for a bioassay or potency assay)



Appendix 3 – What's new (cont'd)

3.2.S.4 Control of the Drug Substance

- Change in the specifications used to release the drug substance **(No major changes)**
  - **<u>Addition of a test</u>:**
    - ✓ <u>Previous version:</u> → ***NC (no condition)***
    - ✓ <u>Current version:</u> → ***Level III (2 conditions)***

<u>Conditions</u>:

1. No change in the limits outside the approved ranges for the approved assays
2. The addition of test is not to monitor new impurities species.




Appendix 3 – What's new (cont'd)

3.2.S.5 Reference Standard

- Qualification of new lot of Reference Standard against the approved Reference Standard → Level III (Conditions 1-2)

- *Extension of reference standard shelf life → Level III (Condition #2)*

Conditions:

1. Qualification of the reference standard is performed according to the approved protocol (i.e. no deviation from the approved protocol).
2. The reference standard is not for a bacterial or a viral vaccine or for a product in lot release group 2.



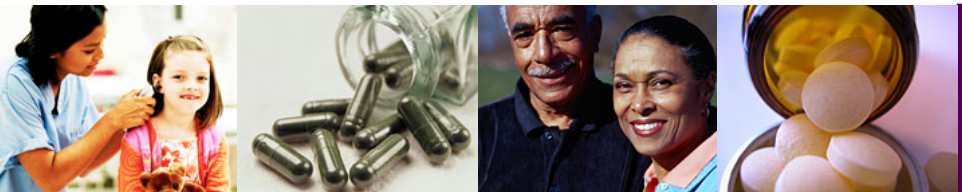

Appendix 3 – What's new (cont'd)

3.2.S.6 Container Closure System (no major changes)

- Change in the *primary* container closure system(s) for the storage and shipment of the drug substance → Level III (1-2)

Conditions:

1. The proposed container closure system is at least equivalent to the approved container closure system with respect to its relevant properties.
2. The change does not concern a sterile drug substance.



Appendix 3 – What's new (cont'd)

3.2.S.7 Change in in the shelf-life of the DS or for a stored intermediate of the DS (no major changes)

- If based on interim results → NC
- If based on full long term results → Level III (4 conditions)

1. No changes to the container closure system in direct contact with the drug substance with the potential of impact on the drug substance; or to the recommended storage conditions of the drug substance.
2. The approved shelf life is at least 24 months.
3. Stability data were generated in accordance with the approved stability protocol.
4. Significant changes (as defined in ICH's Q1A guideline) were not observed in the stability data.




Appendix 3 – What's new (cont'd)

3.2.P.1 Description and Composition of the Drug Product (no major changes)

- Addition of a dosage form or change in the formulation
- Change in fill volume (same concentration, different volume)
- Change in the concentration of the active ingredient
- Addition of new presentation
- Change to an adjuvant
- Change to diluent




Appendix 3 – What's new (cont'd)

3.2.P.3 Changes involving a drug product manufacturer/ manufacturing facility

- Replacement or addition of a drug product manufacturing facility (includes primary packaging facility)

Previous version: → ***Supplement***

Current version: → ***NC (4 conditions)***

1. The formulation/filling facility is a Health Canada approved facility.
2. No change in the composition, manufacturing process and DP specifications
3. No change in the container/closure system
4. The same validated manufacturing process is used




Appendix 3 – What's new (cont'd)

3.2.P.3 Changes involving a drug product manufacturer/ manufacturing facility

- Effect on the *existing* drug products in a DP manufacturing facility, involving:

a) Conversion of a DP manufacturing facility from single-product to multi-product

Previous version: → ***Supplement***
Current version: → ***NC (No condition)***

b) Conversion of formulation and filling area(s) from campaign to concurrent for multiple product manufacturing areas → ***NC (1 condition)***




Appendix 3 – What's new (cont'd)

3.2.P.3 Changes involving a drug product manufacturer/ manufacturing facility

- Scale-up *or scale-down* of the manufacturing process at the formulation/filling stage → **NC (4 conditions)**

- ***Product-contact*** equipment change from dedicated to shared → **NC (No condition)**

- Addition of a new scale bracketed by the approved scales ***or scale-down*** of the manufacturing process → **Level III (4 conditions)**




Appendix 3 – What's new (cont'd)

3.2.P.3 Changes involving a drug product manufacturer/ manufacturing facility

- Change in the controls (in-process tests and/or acceptance criteria) applied during the manufacturing process ***(No major changes)***

- *Major* changes to the following process validation protocols: introduction of product into an multi-product facility, protocol for the cleaning of equipment (e.g., change in the worst-case scenario during cleaning validation process)
  - Previous version: → **NC (1 condition)**
  - Current version: → **NC (No condition)**




Appendix 3 – What's new (cont'd)

3.2.P.4 Control of Excipients (no major changes)

- Change in manufacture of a *biological* excipient → **Level III (2 conditions)**
- Change in supplier of an excipient of non-biological origin or of biological origin (excluding human plasma-derived excipient) → **Level III (condition 1)**
  - Previous version: **Level III (Supp. Data 3-4)**
  - Current version: **Level III (Supp. Data 3)**

Supporting data:

4. Information on the manufacturing process and on the controls performed at critical steps of the manufacturing process and on the intermediate of the excipient.




Appendix 3 – What's new (cont'd)

3.2.P.5 Control of Drug Product (same as for DS)

- Changes affecting the QC testing site **(release and stability)**:

Previous version: ***→ Level III (1 condition)***

- Could be filed as Level III or NC depending if the test transferred was a bioassay and the new testing site was under the same QA/QC oversight (i.e. with the same QA/QC signing authority)

Current version: ***→ NC (no condition)***

- A NC is required for the transfer of all non-pharmacopoeial assays
- Transfer of pharmacopoeial assays can be filed as Level III (except for a bioassay or potency assay)




Appendix 3 – What's new (cont'd)

3.2.P.5 Control of Drug Product (same as for DS)

- Change in the specifications used to release the drug product ***(No major changes)***
  - Addition of a test:
    - ✓ Previous version: → ***NC (no condition)***
    - ✓ Current version: → ***Level III (2 conditions)***

1. No change in the limits outside the approved ranges for the approved assays
2. The addition of test is not to monitor new impurities species.




Appendix 3 – What's new (cont'd)

3.2.P.6 Reference Standards or Materials

- (same as for DS)

3.2.P.7 Container Closure System

- Modification of a *primary* container closure system (e.g., new coating, adhesive, stopper) → **AN (conditions 1-3)**

1. No change in the type of container closure or materials of construction.
2. No change in the shape or dimensions of the container closure.
3. The change is made only to improve quality of the container and *does not modified the product-contact material.*




Appendix 3 – What's new (cont'd)

3.2.P.8 Change in shelf life for Drug Product

- If based on interim results → NC
- If based on full long term results → Level III (4 conditions)

1. No changes to the container closure system in direct contact with the drug product with the potential of impact on the drug product; or to the recommended storage conditions of the drug product.

2. The approved shelf life is at least 24 months.

3. Stability data were generated in accordance with the approved stability protocol.

4. Significant changes (as defined in ICH's Q1A guideline) were not observed in the stability data.




Appendix 3 – What's new (cont'd)

3.2.P.8 Change in the post-approval stability protocol of the Drug Substance or Drug Product, involving:

- Major change to the post-approval stability protocol or stability commitment, such as *deletion of a test*, *replacement of an analytical procedure*, *change in storage temperature*.

Previous version: → ***NC (No condition)***

Current version: → ***Level III (2 conditions)***

1. For the replacement of an analytical procedure, the results of method validation demonstrate that the new analytical procedure is at least equivalent to the approved analytical procedure.
2. The new analytical procedure maintains or tightens precision, accuracy and sensitivity.




Appendix 3 – What's new (cont'd)

3.2.P.8 Change in the post-approval stability protocol of the Drug Product, involving:

- Addition of test(s) into the post-approval stability protocol
  → ***Level III (1 condition)***

<u>Conditions</u>:

1. The addition of test(s) is not due to stability concerns or to the identification of new impurities.




Conclusion

- Incorporates Health Canada life-cycle approach & sound science/risk management principles
- In line with International initiatives/harmonization
- Takes into account advances in technology (PAT/QbD, Parametric Release)
- Provides transparency, clarity, and detail
- Facilitates classifying changes/data requirements (several examples provided)




Acknowledgment

Post-NOC quality sub-working group (Biologics):

Anthony Ridgway
Harold Rode
Janice Campbell
Andrei Barbacaru
Christina Bellotti
Kiran Nath
Stephanie Hardy
Hugo Hamel




QUESTIONS

????