Post-Notice of Compliance (NOC) Changes

CAPRA Dinner Meeting
August 2010
Joyce Pon - TPD



Canada

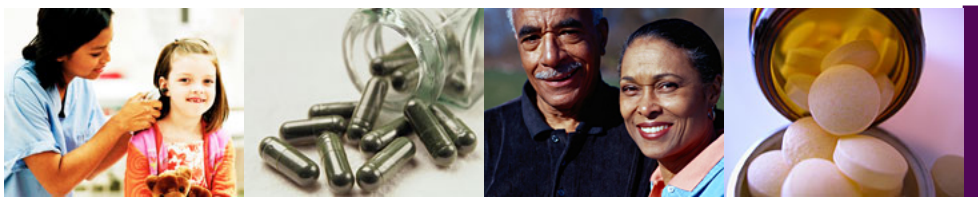
Outline

- Post-NOC Changes guidances
- Highlight the Major changes
- Screening Experience Since Implementation




Post-NOC Changes Guidances

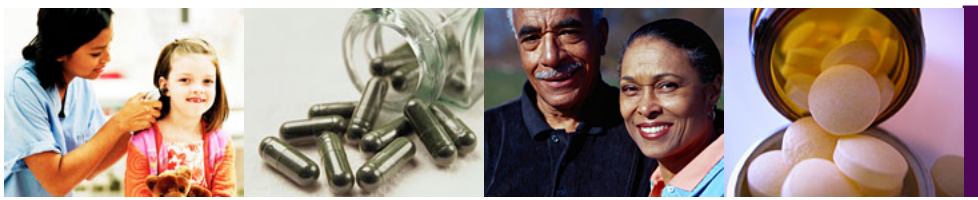
- Framework Document that provides overarching authorities, general description of the proposed reporting categories, drug submission filing and contact information
- Safety and Efficacy Guidance Document
- Quality Guidance Document
  - Appendix Tables
    - 1- Pharmaceuticals (TPD and VDD)
    - 2 - Veterinary Drugs – NEW (supplementary to Appendix 1)
    - 3 - Biologics
    - 4 - Radiopharmaceuticals



Post-NOC Changes Guidances

Scope and Application:

- changes to new drugs that have received an NOC pursuant to section C.08.004 of the *Food and Drug Regulations*
- pharmaceuticals, biologics, and radiopharmaceuticals for human use
- pharmaceutical, radiopharmaceutical and certain biotechnological products for veterinary use
- applies to those submissions for which a NOC has been recommended but issuance of the NOC has been placed on hold



Post-NOC Changes Guidances – cont'd

Oversight Required prior to implementation:

Level I (300 days & 180 days*) –Safety and Efficacy & Quality

Level II (90 days) Safety and Efficacy & Quality

Level II (120 days) Safety and Efficacy

Oversight **not** required prior to implementation:

Level III - Annual Notification

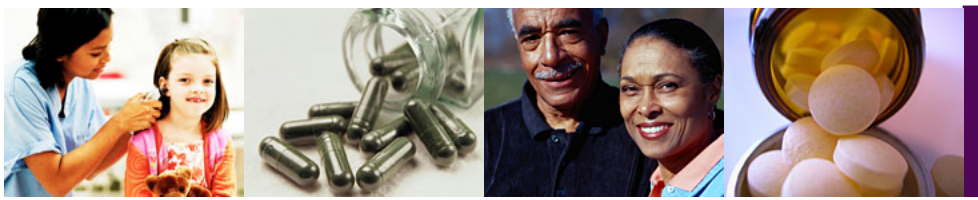
Level IV - No notification req'd –Quality only




Highlight the Major Changes

Major changes:

- replaced the default date with a target date for Level II (90 day) changes;
- addition of Level II (S&E) (120 day) change with target date;
- retention of the Level IV change category -Quality sub-components only;
- new Appendix for Veterinary drugs (Appendix 2);
- electronic Level III form developed and posted;
- CPID and PM not required to be submitted for Level III changes.



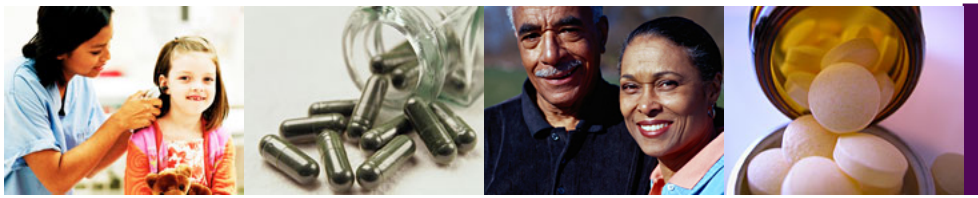
Screening Comments - Organization and Completeness of Submissions

Cover Letter

Safety and Efficacy changes -clearly indicate whether Level II (90 day or 120 day) or clarification request will be sent

Quality changes – see slide 10 for example of table

- clearly indicate what changes are being filed referencing the corresponding section of the Guidance (i.e. change #);
- clearly indicate which relevant conditions have been met;
- clearly indicate whether all supporting data have been provided and ensure the data or rationale for absence is appropriately organized as per CTD format and location in submission (e.g. description of batches located under P.5.4).



Screening Comments - Organization and Completeness of Submissions

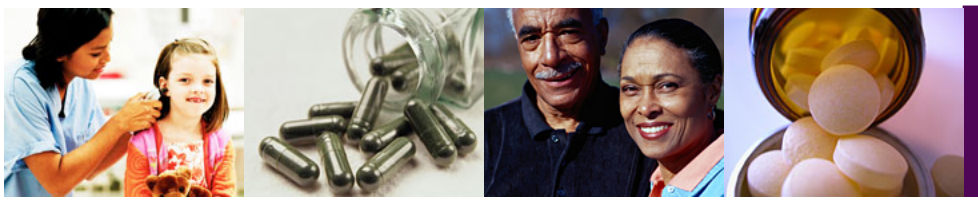
- SDN is sent by TPD if supporting data is not provided in the corresponding CTD section of the submission or clarification is required of its location;
- distinguish the NC from any other highlighted text (e.g. Level III change or Level IV);
- identify each NC if multiple changes are being proposed or if one NC change stems from another change (e.g. a revision to test specification where a new site of manufacture is being proposed)
- supporting data submitted “where applicable” (e.g. inner/outer labels only if affected by the change)




Screening Comments – Appropriate Classification of Quality Changes

- changes are not accurately classified with the conditions to be fulfilled

  (e.g. addition of a drug substance manufacturing site involving production of starting material, intermediate, or drug substance can Level I, Level II or Level III depending on condition to be fulfilled)
- All conditions and supporting data should be addressed by stating “Not applicable” if that is the case



Example of Quality NC Screening Clarification

Notifiable Change for Brand Name (common name), Control No. ######

In accordance with section 2.2.3.3 of the Post-NOC Changes Framework Document and section 3.1 of the Post-NOC Changes Quality Document, the following information should be clearly indicated in your submission. *To facilitate the screening process, please indicate this information in your cover letter for future filings.*

1. Please state the nature of the change(s) being filed and the corresponding section of the guidance document.

2. Please indicate whether all relevant conditions have been met to qualify as a level II change as outlined in that section of the guidance.

3. It should be clearly indicated whether all supporting data listed in that section of the guidance has been included in the submission and organized as per CTD for Quality (Chemistry and Manufacturing). If any supporting data is not provided as outlined, a rationale explaining the reason should be listed.

To facilitate screening and review, you may wish to consider using a tabular format in your cover letter, as suggested below:

Description of Change	Conditions to be Fulfilled	Conditions Fulfilled	Supporting Data Required	Supporting Data Provided	Location in Submission

4. For situations where multiple changes are being proposed, or a level II change stems from another change (for example, a revision to test specification where a new site of manufacture is being proposed), each NC change should be clearly identified, as above.

In order for your submission to be acceptable for review, a complete response must be received within **XX** days of the date of this **facsimile/email.**



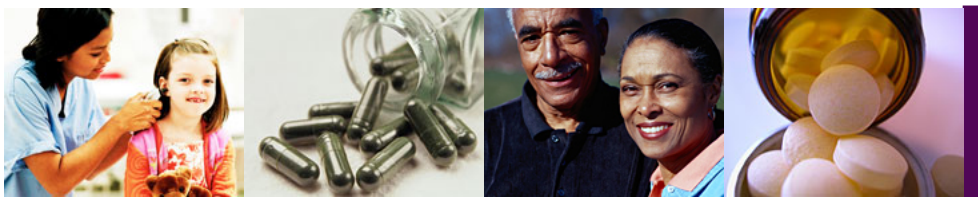

Screening Comments – GMP Compliance

Notice (January 22, 2010) Submission Filing Requirements - Good Manufacturing Practices (GMP)/Establishment Licences (EL)

For drug submission purposes, "evidence of GMP compliance" would include a:

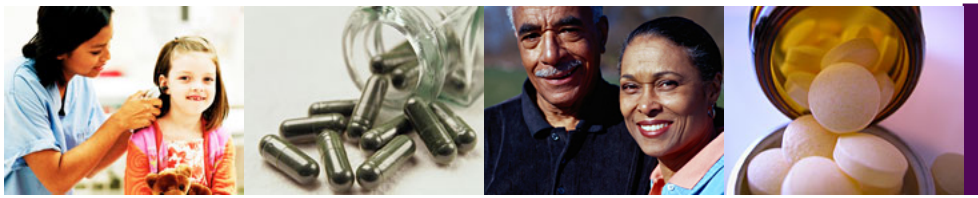
- Valid Health Canada EL, or
- Current GMP compliance rating issued by the HPFB Inspectorate (TPD) or rationale for omission (BGTD)

This requirement is be applicable to all (NDSs), (ANDSs), (SNDSs), (SANDSs), (NCs) submitted for review to TPD/BGTD. Manufacturers need to have a satisfactory rating for their site for the particular dosage form.



Screening Comments – GMP Compliance – cont'd

- Note: GMP required for testing (drug substance release) for the drug product manufacturer whether or not the substance is sterile;
- refer to table - Summary of Good Manufacturing Practices (GMP) Requirements for Drug Submission Purposes



Screening Comments – Revision in Final Quality Guidance (Appendix 1 & Appendix 6)

Since the release of these documents via email on September 30, 2009, the following corrections have been made to the Post-NOC Changes Quality document:

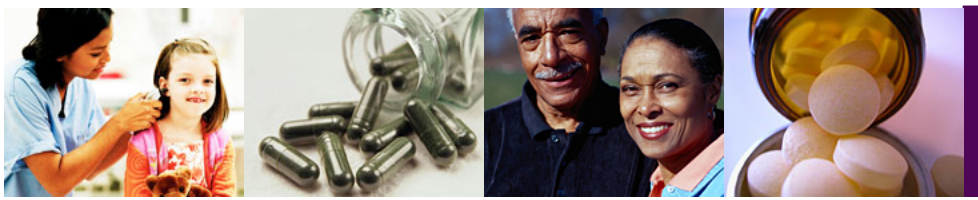
1) Appendix 1 - corrections in the supporting data requirements for changes #2b and #27d,
2) Appendix 6 - addition of "core" weight to the title of the table.

The final version posted on the Health Canada website has been corrected.




Screening Comments – cont'd

- For Clinical Changes (NC or SNDS):
  - PSURs should only be provided if they support a PM change, otherwise, submit all PSURs to MHPD in future;
  - If possible, Company Core Data Sheets (CCDS) should be provided to facilitate review;
- For Quality Changes (NC or SNDS):
  - signed and dated specifications are required.



Screening Comments – cont'd

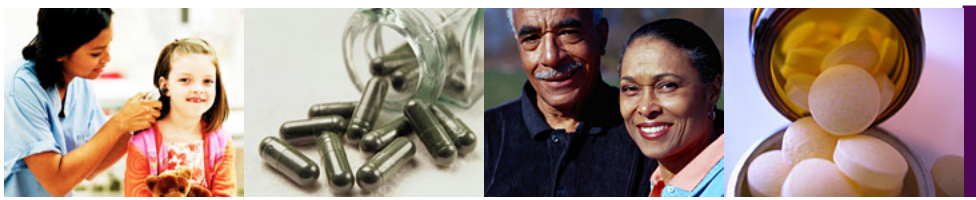
Pre-submission enquires

(Section 2.2.2 of the Framework guidance)

- classification of a proposed change
- supporting documentation

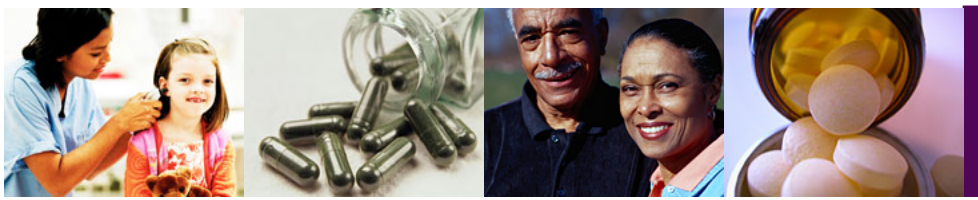
Contact information

- *Guidance for Industry: Management of Drug Submission (Human drugs)*
- *Guidance for Industry: Management of Regulatory Submissions (Veterinary drugs)*



Future Revisions to Post-NOC Changes

- Review every 2 years as per *Good Guidance Practices;*
- Review would consider any stakeholder comments received during this period;
- Certain revisions such as for consistency and typographic errors can be made without consultation;
- Extensive revisions that include changes to approach in risk classification would require external consultation.



Thank You

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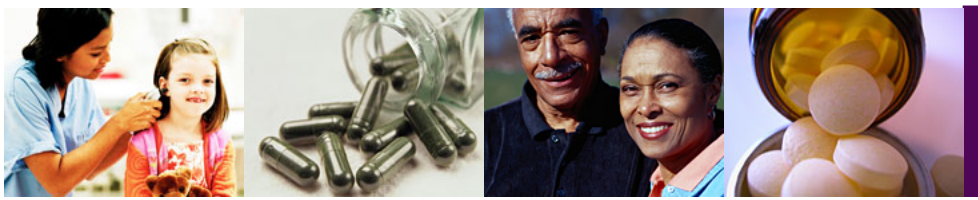

Overview of the post-NOC changes Quality guidance document - Pharmaceuticals

CAPRA Dinner Meeting
August 2010
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Contact Information:

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August 2010
CAPRA Dinner Meeting

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

Hugo Hamel
Senior Biologist/Evaluator, BGTD



Canada

Outline

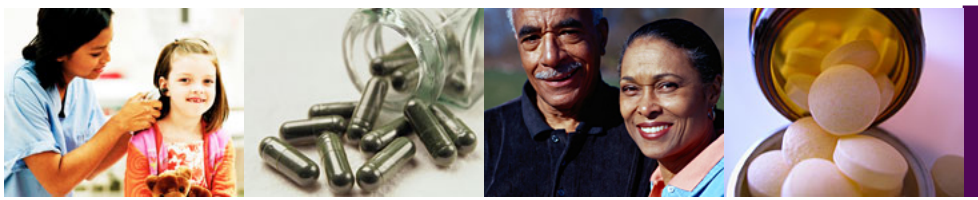
- Post-NOC Changes Quality Guidance - Biologics: Points to Note
- Appendix 3 (Biologics) – Clarification / Additional Guidance




PNOCC Quality guidance document – Biologics – Points to Note

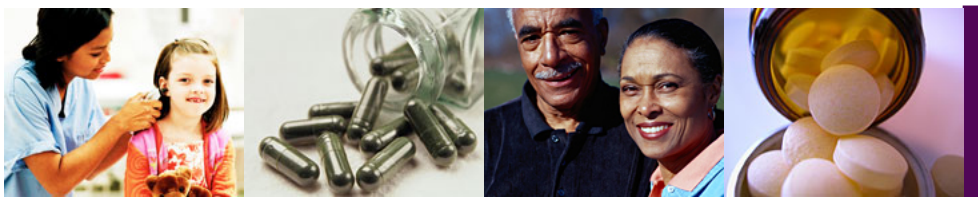
- *Conditions:*
  - All conditions must be met in order to file the change at the proposed Level of filing
  - If any of the conditions outlined for a given change are not fulfilled, the change is considered the next higher level

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



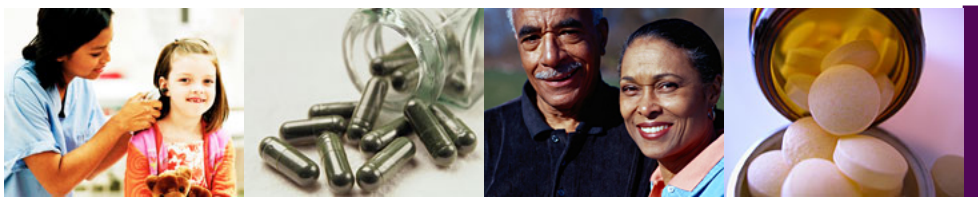
PNOCC Quality guidance document – Biologics – Points to Note

- *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



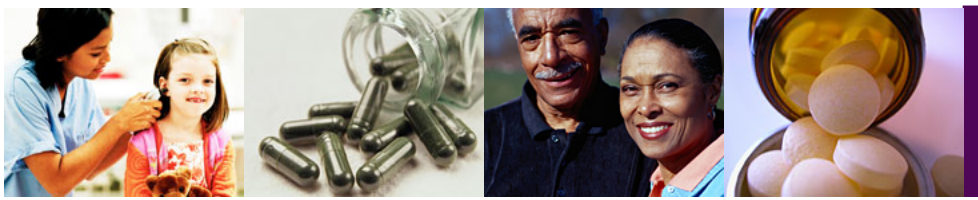
PNOCC Quality guidance document – Biologics – Points to Note

- *<u>CPID and Product Monograph</u>:*
  - If the CPID or PM is impacted by the implementation of a Level III or Level IV change, 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
- *<u>Multiple changes</u>:*
  - It is allowed to bundle these changes
  - Indicate where the changes are related
  - Describe any association between the proposed changes




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 – Clarification

- ***<u>New sites on the DEL before filing</u>: Not required!!!***

3.2.S.2 Manufacture

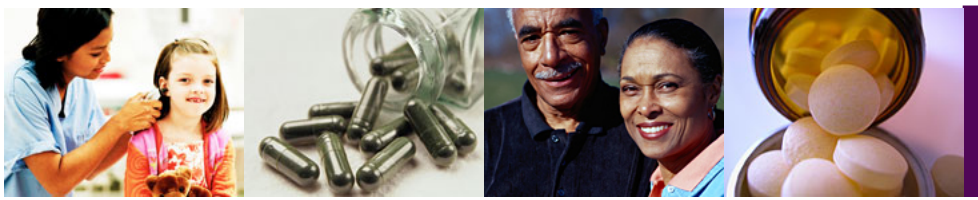
- Replacement or addition of a manufacturing facility for the bulk drug substance, or any intermediate of the drug substance

3.2.P.3 Manufacture

- Replacement or addition of a manufacturing facility for the drug product (including primary packaging facility)
- Replacement or addition of a secondary packaging facility; a labelling/storage facility; or a distribution facility

<u>Supporting data</u>:

1. (1.2.5) GMP and E/L information. *Confirmation that the proposed manufactured site is listed on the Canadian Establishment Licence of the sponsor/manufacturer and/or confirmation of a satisfactory GMP rating by the Inspectorate is no longer required*



Appendix 3 – Clarification

3.2.S.4 Control of the Drug Substance (same for DP)

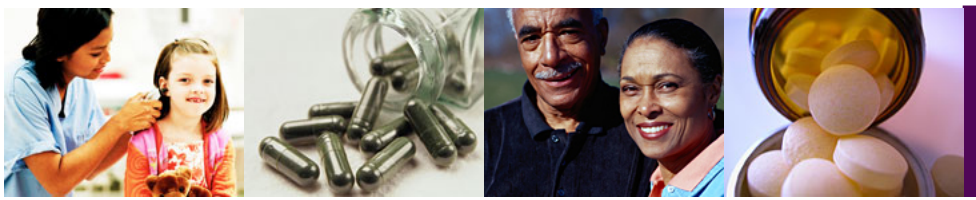
- Changes affecting the QC testing site **(release and stability)**:

Draft #2: → ***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)

Final 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 or Level IV (except for a bioassay or potency assay)



Appendix 3 – Additional Guidance

Change in testing sites:

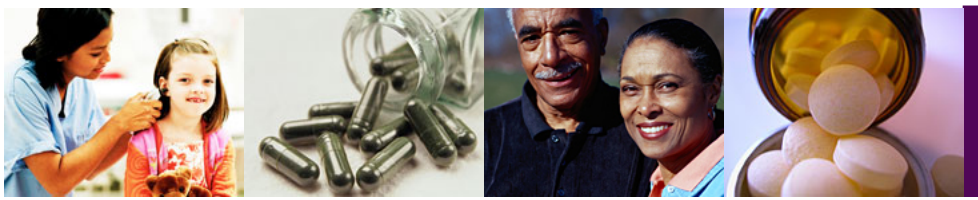
- Change in in-process control testing site → ***Level III (6 conditions)***
  - Same conditions as for change in in-process controls performed at critical steps.
  - No change in the in-process control limits outside of the approved ranges.

- Change in raw material testing site → ***Level III (1 condition)***
  - No change in specifications of the raw material outside of the approved ranges.

- Change in excipient testing site → ***Level III (1 condition)***
  - No change in the specifications of the excipient or drug product outside of the approved ranges.

Supporting data:

1. (1.2.5) Evidence that the new company/facility is GMP compliant.



Appendix 3 – Additional Guidance

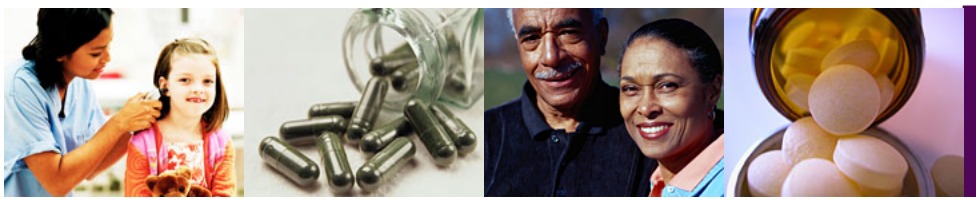
3.2.P.3 Changes involving a drug product manufacturing facility

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

Draft #2: → ***Supplement***

Final version: → ***NC (4 conditions + 1 condition)***

1. The formulation/filling facility is a Health Canada approved facility (for the same sponsor).
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
5. The newly introduced product is in the same family of product(s) or therapeutic classification as the one of those already approved at the site and uses the same filling process/equipment.



Appendix 3 – Additional Guidance

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

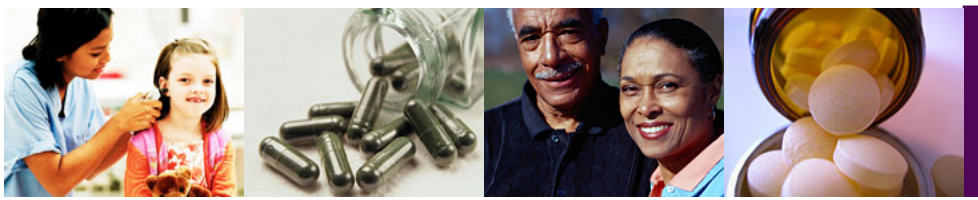
- Replacement of the sterility testing by the container/ closure system integrity testing → ***Level III (1 condition)***

Conditions:

1. The method used to demonstrate the container/closure system integrity has already been approved as part of a previous application (e.g., NDS, S/NDS, NC).

Supporting data:

1. (P.8.2) Updated, QC approved post-approval stability protocol (or where applicable, the final version of the protocol to be signed by QC after HC approval) and stability commitment.
2. (P.8.2) Justification of the change to the post-approval stability protocol or stability commitment.



Appendix 7: Examples of Level IV changes - Clarification

- *The following two changes are only applicable to biologics and radiopharmaceuticals*

  - With the exception of a potency assay or a bioassay, transfer of the QC testing responsibilities for a pharmacopoeial assay to a different facility within the same company.
  - With the exception of a potency assay or a bioassay, transfer of the QC testing responsibilities for a pharmacopoeial assay to a different company listed on the sponsor's establishment licence.




Thank you

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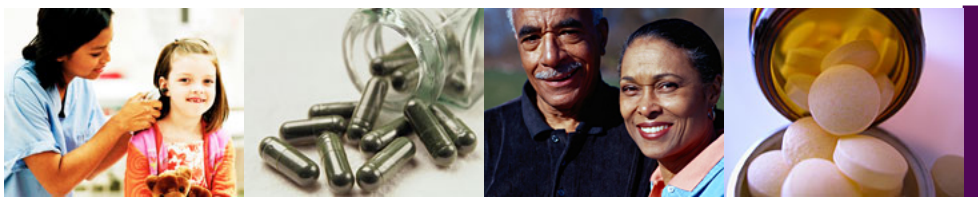


Post-NOC Changes: Safety & Efficacy

CAPRA Dinner meeting
August 2010
Lisa Kelly - TPD



Canada

Overview of S&E Presentation

Discussion of :

- the new criteria for categorizing submissions;
- the new recommendations re supporting documentation

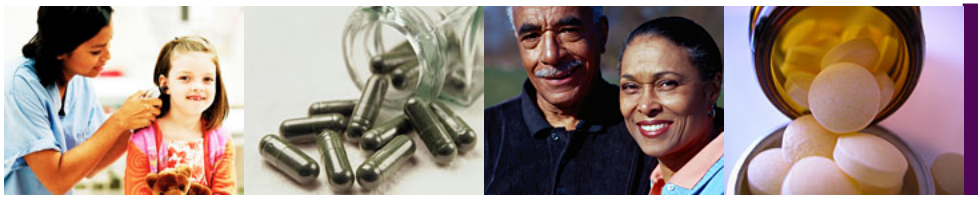



New Criteria for Categorization

-Revised criteria by which to categorize changes to PM / label:

i.e. now explicitly and consistently based on risk-management principles

-In contrast to old criteria (ie from 1994 NC policy), which effectively divided SNDSs from NCs based on which PM sections were being revised



Problems with 1994 “NC” Policy

- NCs tended to be wrongly seen as of lesser importance and requiring lesser work…..which was reinforced by a shorter time-line not tied to urgency

- Classification primarily by PM section resulted in inconsistencies

  eg if a safety update included warning text in Dosage & Admin, it became an SNDs




Revised Criteria:

Shorter review Timeframe = Changes about **PROBLEMS**
ie "improving risk management" e.g. identifying, characterizing risk; adding / revising Warnings or other instructions/recommendations (ie "Conditions of Use")
= Level II (90 days)

Longer review Timeframe = Changes about **POSITIVES**
ie the potential to **increase exposure (population or individual)** e.g. new indications, new route of admin, safety claims, new dose
= Level 1 (SNDS) *




Further Revision to Categories

? Sponsor asked: What about those PM changes which arguably fit neither of the two categories?

ie changes which primarily add information, neither

a) managing risk (ie therefore in some way altering existing “conditions of use” text), nor

b) potential to increase exposure via claims etc

eg (some) changes to DRUG INTERACTIONS, or pre-clinical data, or OVERDOSE




Further Revision to Categories

In the strictest sense, <u>every single statement in a PM</u> that is not about a PROBLEM could automatically be classified as a POSITIVE

ie nothing in between “Shorter review timeframe” vs “Longer review time-frame”

But, the pragmatic reality is that it is not feasible to categorize as SNDSs all changes that are not about risk-management …thus, the results is “tweeners”




Further Revision to Categories

Thus, what to do with changes which can be argued to fit neither

-RISK MANAGEMENT (PROBLEM) nor

-NEW CLAIM / MORE EXPOSURE (POSITIVE),

…..but for which oversight is still required?

Solution: for these “tweeners”, a middling timeframe of 120 days was suggested, as a sub-set of Level II




Final Revised Criteria:

Thus, now three Categories

Shorter review Timeframe = Changes that are about **managing risk** (identifying, characterising, making recommendations etc.) **= Level II (90 days)**

Longer review Timeframe = Changes with the potential to **increase exposure** (e.g. new indication, safety claims, new dose) = **Level I Supplement 300 days***

Middling Timeframe = Changes requiring oversight, but which fit neither of the above = **Level II (120 days) …. = tweeners**




Level II (90 days): Risk Management

Examples:

-new CONTRAINDICATION, WARNING, PRECAUTION, or clarifying / strengthening existing text;

-identifying / characterising adverse event, or recommendations in managing the risk;

-alteration to conditions of use, for risk management

-risk management concerns resulting from a drug interaction study;

-new overdose symptoms / treatment added;




Level I Supplements: Examples

-**a new indication has been added** (for VDD: addition of new species) or revision to INDICATION other than for risk management;

-**change to text anywhere in PM referring to potential benefits/claims of the drug*****, whether efficacy or side-effects, such as:

-PM revisions related to studies of specific sub-populations exposed to recommended therapeutic dosing (eg Special Pops);

-changes to Mechanism of Action of the drug; change to CLINICAL TRIALs which results in a new claim.

-**any diminishment to cautionary/risk management text** anywhere in the PM***




Level II (120 Days) “Tweeners”

Oversight required, but changes deemed to not alter conditions of use / affect advertising

Examples:

- changes to OVERDOSE other than symptoms/treatment;
- addition /change to DRUG INTERACTION that is not considered to alter conditions of use / risk management ie no precautionary wording, but also insufficient for a claim, because not therapeutic dose / duration)
- changes made to the Pharmacokinetics section in ACTION AND CLINICAL PHARMACOLOGY that do not alter conditions of use, or imply benefit/claim;
- REFERENCES: addition that does not expand claims.




Real-Life Examples

- Update to the CLINICAL TRIAL section of the PM with data to reflect longer follow-up times in studies.

- OVERDOSAGE: Increase to the stated highest dose that patients have been treated with in clinical trials

- Remove restriction that drug must be taken with fat-free meal




Elimination of “default” date

Replaced the 90 day **default** date (as NCs), with 90 day **target** date, for Level II (90 day) changes

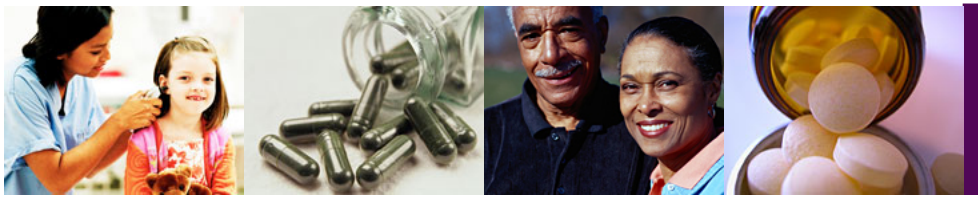
Since Level II (90 day) changes are about managing risk, that means: If review cannot be completed in the target time, a judgement call is required by the 90 day target date, as to whether interim PM changes are needed ie until the review can be completed.




Re Supporting Information

- Part of the intent is to minimize time spent by HC reviewers requesting, and waiting for, information that provides essential context

- The more complete the initial submission, the fewer delays, as the entire picture is needed for optimal regulatory decision-making.



Re Supporting Information

"Contextual Para" on Documentation:

"Regulatory decision-making is optimal when contextualized via a variety of information beyond the data itself…"

- This "contextual information" is not a requirement for screening; rather, it is anticipated that **the sponsor will not be silent on the issue**

ie EITHER provide the information, OR acknowledge the absence, and why

-Case-by-case judgement call by review staff as to whether an absence is a problem in an individual file




Re Supporting Information

Common to Level I (Supp.) and Level II (NC) includes:

- clinical and /or non clinical study data e.g. efficacy, PK, PD, epidemiological, pharmacovigilence, studies in PSURs
- data other than from study reports: e.g. PSURs, review /reports / analysis of safety concerns; publication-only studies; real-world drug use information; abstracts;
- copy of most recent core data safety sheet;
- copies of most recent labelling from other major ICH jurisdictions;
- copes of pertinent communications with these agencies.
- other relevant info: e.g. sponsor rationales; RMPs; expert opinions; reviews; advisory transcripts;




Re Supporting Information

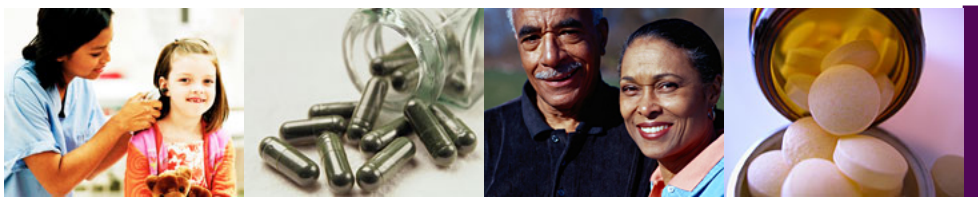
Specific to Level I (300 days, 180 days)

- where available, copies of any relevant foreign review reports, Q & A etc from other major ICH jurisdictions
- summary of substantive issues raised by other jurisdictions and how they were resolved (or statement that there were none)

Specific to Level II (90 days)

-any communications to health professionals/patients (OR explicit statement confirming lack)

- Most recent PSURs (cumulative & non-cumulative) if the risk issue in question is addressed in the PSUR



Thank You

Contact Information:

Safety and Efficacy WG member:

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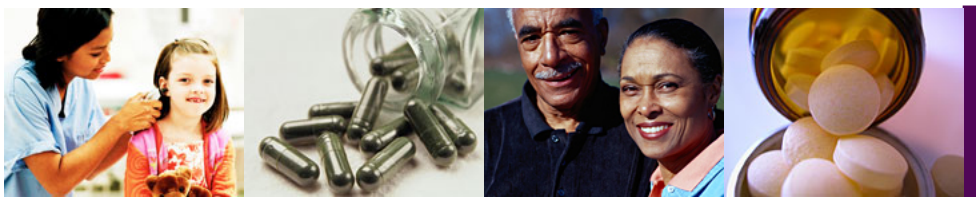

QUESTIONS

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