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Post-NOC Changes

Safety and Efficacy

A Sponsor Perspective

CAPRA, March 1, 2010, Toronto

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Scope

- C.08.003(1) of the Cdn Food and Drug Regulations states
  - ..no person shall sell a new drug in respect of which a NOC has been issued to the manufacturer…, if any of the matters specified in subsection (2) are SIGNIFICANTLY DIFFERENT from the information…contained in the NDS…
- If the information is significantly different, then an SNDS is required.
- The regulations do not speak to Notifiable Changes or Annual Updates.
- The requirements for Levels 2-4, enable Health Canada to determine if the change is significantly different.
- If they are significantly different, then they revert to Level 1.
- There is a significant disconnect here between the Regulations and the Guidance.
- It would be helpful if regulations specifically addressing Notifiable Changes and Annual Updates were available.

Notifiable Changes

- The concept of a Notifiable Change was that it was a change for which approval was not being sought (nor under regulation was required) for a New Drug. Health Canada was notified of the intended change and allowed 90 days to ensure that they agreed that the change did not require an SNDS.
- **All Level 2 changes should not be implemented by the sponsor until a No Objection Letter (NOL) has been issued.**
- As opposed to being a Notification, Level 2 has now become a pre-approval change.

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Products on Hold

- This guideline clarifies that it applies to submissions for which an NOC has been recommended, but issuance has been placed on hold.
  - Generic Applications for ANDSs
  - Prescription to Nonprescription NDS/SNDSs
  - Biologics awaiting an OSE
- This has been the policy of Health Canada, but it is nice to see this clarification in writing.

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Level 1 Changes (SNDS Required)

- Any change to the existing test of the Product Monograph that refers to any potential benefits of the drug, implicit or explicit, including claims regarding the safety profile or efficacy. This includes changes in text with reference to sub-populations and any reference to possible claims regarding side effects.
  - Consider the approval of a drug for a cancer indication based on 3-year data. Five-year data becomes available. The data in the Product Monograph needs to be updated describing the study. No additional implicit or explicit claims are involved.
    - Does this require a SNDS?
  - Consider an update regarding safety. Wouldn't any update regarding safety (unless it simply lists an ADR) be a reference to "possible claims regarding side effects"?
    - Does this require an SNDS

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Level 1 Changes (SNDS Required)

- A new indication has been added, including reintroduction of an indication that had received an NOC and was subsequently withdrawn.
- Consider: Product x is withdrawn from the market due to low sales volume and lack of a distributor. The product is purchased by an existing Canadian company.
  - Traditionally, this product would be put on the market again with an Administrative NDS.
  - Does this now mean that Administrative NDS's to change a product from company A to company B for withdrawn products is no longer possible?
  - If the product was withdrawn for issues other than safety, what is the purpose of this requirement?
  - What about the re-introduction of a Dosage Form that was removed from the market for sales reasons? Would an SNDS be required?

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Level 1 Changes (SNDS Required)

- Any change regarding the mechanism of action THAT RESULTS IN AN EXPLICIT OR IMPLICIT CLAIM.
- Consider: How is the decision made that a change results in an explicit or implicit claim? There will likely be battles within companies regarding whether a particular modification of the mechanism of action results in such a claim, and therefore whether an SNDS is required.
  - Option will be to request clarification one by one, which is not efficient.
  - Probability will be that most changes in mechanism of action will eventually be required to be Level 1

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Level 1 Changes (SNDS Required)

- Any information to the Clinical Trial Section of the Product Monograph WHICH RESULTS IN A NEW CLAIM, EXPLICIT OR IMPLICIT.
- Consider: The Product Monograph guidelines indicate that clinical trials should be summarized including primary and secondary endpoints and their statistical significance.
  - You decide to add secondary endpoint information to your Product Monograph in agreement with the new Guideline. The secondary endpoint information makes no new claim.
  - Does this require an SNDS?
  - Will all Divisions of TPD/BGTD interpret this the same way?

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Level 1 Changes (SNDS Required)

- An existing route of administration, dosage form and/or strength has been deleted due to safety reasons.
- Consider: A decision is made to remove a dosage form for reasons unrelated to safety, e.g., the IR version of a antihypertensive medication.
  - This can be done without an NDS
- Consider: A decision is made to remove the IV route of administration and its associated dosage form.
  - This can be done without an NDS
- HOWEVER: Putting these back on the market requires an NDS, once they are taken off?

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Level 2 Changes (Require Notifiable Change)

- There are now two levels
  - Level 2 (90 Day)
  - Level 2 (120 Day)
- 90-Day NCs get priority
- These are the equivalent of Changes Being Effected (CBE) submissions in the US that have review times of 0, 30, 60 or 90 days associated with them
- How can we rely that with the expansion of the category to include 120 days for review, Health Canada will adhere to the target?

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Level 2 (90 Day) Changes

- A change that has the potential to improve the management of risk
  - The identification or characterization of any AEs, addition or strengthening of risk management measures for the AE.
  - The identification of subgroups or conditions of use, for which the benefit to risk profile has the potential to be less favourable.
  - The addition or strengthening of risk management measures.

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Level 2 (90 Day) Changes

- Example: An existing indication has been altered for risk management purposes including reduction in scope.
- Consider: A drug is approved for use in adults to treat X. Risk management information requires the indication to be reduced so that it is indicated for females 45 years of age and older. Do we correctly understand that this can be done with 90 day Notifiable Change?

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Level 2 (120 Day) Changes

- These changes are clear in the guideline, with the exception that there is a judgemental decision regarding the change "not altering the conditions of use"
  - How will industry determine in their context whether the condition of use has been altered?
  - Where will the decision be made that the conditions of use are altered?
    - Screening / Reviewing Division?
  - Will all Divisions in TPD interpret this in a consistent manner?
  - Will all Divisions of BGTD interpret this in a consistent manner?
  - Will TPD/BGTD interpret this in a consistent manner?

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Level 3 Changes (Annual Notification)

- Any change to the label that is not expected to impact the safety, efficacy and/or effective use of the drug.
  - Layout of the label (contrast, artwork, font, position)
  - Changing a publication from “in press” to published
  - Standard phrasings on labels, e.g., “Keep out of reach of children”
  - Sponsor contact information
- Consider: Does this include trademark information.
- Copy of the label is required to be sent. In this context is label meant to include Product Monograph?

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Level 4 Changes (Record of Change)

- Not addressed for safety or efficacy.
- Potentially trademark changes could occur here, but it is difficult to imagine that a change in spelling is a level 3 change and a trademark issue a level 4 change.
- It would be helpful to sponsors if there were clarity that there are no scenarios that have been identified at this point in time that would serve as a Level 4 change to a Product Monograph.
- Consider: A company produces a Tradename for their dosing regimen "The 3 Step Dose Ladder" and adds this to their Product Monograph as a Level 4 change
  - Is this allowed?
  - What does it mean for PAAB?

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Generic Companies

- Generic companies are supposed to file using the same level as would apply to the innovator.
- How would a generic company be notified that a change has been made by a Notifiable Change.
  - Some of these changes could be significant.
- How are Product Monographs that are posted on Health Canada's web kept up to date?
  - Are revised versions of the Product Monograph filed through NC's updated there?
  - What is timeframe?
  - What about changes that occur in Annual Notifications?
- When will French Product Monographs be added to the website and how will these monographs be kept up to date?

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Pre-Submission Enquiries

- For Level 1 changes, only one clinical study is available or package is based on publications
  - There will be many times that only 1 study is available, e.g, hepatic/renal impairment, mechanism of action, studies in specific subgroups. What is the purpose of having the company call TPD/BGTD each time.
- The clinical trial makes use of an unvalidated endpoint
- The clinical trial does not reach statistical significance for a primary endpoint or an endpoint involved in the change
- The clinical trial made us of a comparator authorized but not available on the Canadian market
- For generic, if CRP is no longer marketed
- For generic, if a strength outside of CRP is required.
- For generic, if non-Cdn CRP is used.

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Comments

- For generic products, why can't Health Canada publish the products for which they will accept non-CRP in a format that is easy to see
  - It seems a black box with not a lot of transparency
  - The information is published on the NOC database, but cannot be searched.
  - Proving which non-CRP you want to use could still be kept company specific.
    - The NOC database does outline which non-CRP was used for approval.

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Contextual Information

- Company core data safety sheet
  - Does this imply that expedited reports of ADRs can be based on core data safety sheet.
  - It is possible that some companies who distribute only in Canada and/or US may not have a core data safety sheet.
- Copies of labels from ICH countries
  - This will involve a lot of translation if we include labels from potentially 25 European jurisdictions
    - Likely UK alone would be sufficient?
- Correspondence with other major regulatory jurisdictions or a statement confirming that such communications have not been required.
  - This may be problematic for some companies, especially with licensing and other considerations.

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Contextual Information – Level 1

- Current status in other jurisdictions
- Reviews (including questions and answers) from other jurisdictions. If no review is available, then a summary of any significant issues raised and how they were addressed.
- If the review is not yet completed in other jurisdictions, a summary of significant issues raised.

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How to Interpret for Certain Kinds of Drugs

- Clorox Toilet Bowel Cleaner with Bleach
- Fantastik Toilet Bowel Cleaner
- Lysol Toilet Bowel Cleaner
- Windex Disinfectant
- Contact Lens Solutions

- I have a hard time getting my head around filing a New Drug Submission for a toilet bowel cleaner.
- I have more difficulty interpreting guidelines on safety and efficacy (and changes in route of administration and stuff) for these products.
- Please can't we get these out of DRUGS in Canada
- The definition of "drug" states that disinfectants used in premises where food is prepared.

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Summary

- Greater clarity is helpful, but there is still a lot of judgement in making many of the clinical decisions.
  - There is potential for different Divisions/Bureau/people to interpret differently
- Disconnect in Regulations and Guidance
  - The requirement to have prior approval of a Level 2 change is not required by regulation.
- Greater transparency in terms of NonCdn Ref Product would be helpful to both the generic and innovative industry.
- Anne on her soapbox – please get toilet bowel cleaners and contact lens solutions out of the New Drug requirements.

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Contextual Information – Level 2 (90 Day)

- Warning letters from other jurisdictions (or a statement that they are not required)
- Most recent PSUR
- Company Core Data Safety Sheet