The Challenge of Change

Working with the Post-NOC Guidances

Biologics Quality

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Regulatory CMC Guidance in Canada (2007)

Today	Tomorrow	Beyond
"Dated" guidances	Updated to reflect current practice	Design Space (ICH Q8)
Small molecules-based	Updated to CTD format	Quality Risk Management (ICH Q9)
Lacking detail	Small molecules, biologics and radiopharmaceuticals considered separately	Quality Systems (ICH Q10)
Lack of harmonization across regions	Vastly increased detail	
	Harmonization increasing	

Regulatory CMC Guidance in Canada (2010)

Yesterday	Today	Tomorrow
"Dated" guidances	Generally reflect current practice	Design Space (ICH Q8)
Small molecules-based	CTD format	Quality Risk Management (ICH Q9)
Lacking detail	Small molecules, biologics, veterinary drugs and radiopharmaceuticals considered separately	Quality Systems (ICH Q10)
Lack of harmonization across regions	Detailed	
	Increased harmonization	

Evolution of Biologics Quality Section General Observations

- The guidance underwent both content and organization improvements from draft 1 to draft 2 to final
- Much industry input was incorporated
- Where sections have evolved, many have introduced:
  - Reduced filing category options
  - Clarified wording
  - Intra-document harmonization
- A few late revisions (after draft 2 comment period) have increased filing categories
- Late introduction of specific pre-filing requirements around establishment licensing has introduced significant implementation concerns

What we liked ….

Then	Now
One stop shopping	One guidance – convenience
Organized according to the CTD – easily navigated	Easy navigation
Biological drug changes no longer force-fit into small molecules guidance	Biologics-specific
Reduced stability data requirements	Further clarification (data points and applicable ICH guidance)
Level 4 is gone!	It’s back!
Positive moves toward harmonization with other regions	Few instances of significant misalignment (except EL)

New Clarifications

- Supporting data sections now clearly state where summary data is adequate for submission/raw data on request. Eg:

Draft 2

(S.2.5) Process validation and/or evaluation studies.

Final

(S.2.5) Summary of the process validation and/or evaluation studies. The complete report with all raw data could be requested during review.

- Stability data requirements are detailed and clear. Eg:

  "results of a minimum of 3 months of accelerated and 3 months of real time/real temperature testing on 3 drug product batches, or longer if less than 3 time points are available (including the zero time point)"

  "Bracketing and matrixing per ICH Q1D if scientifically justified"
- More guidance around diluents
- Reorganization of drug product manufacturing change sections through drafts
- Reorganization of changes to test methods and specifications

New Reduced Requirements

- Production documents are no longer required at time of submission
- New drug product mfg facility may be a Notifiable Change in some cases
- Conversion of a *drug substance* manufacturing facility from single to multiproduct reduced to a Notifiable Change at Draft 2 stage*
- Conversion of a *drug product* manufacturing facility from single to multiproduct reduced to a Notifiable Change at final version*

* Aligns with equipment changes from dedicated to shared

New Increased Requirements

- Notifiable Changes are no longer a default approval – too soon to gauge impact
- Transfer of non-pharmacopoeial testing was L3 (except for bioassays) – now L2
- New sites on the DEL before filing.

Where we had queries……

- Would the new guidance be too prescriptive (loss of scientific flexibility)?
  - We are not seeing this ….. yet.
- Is there an opportunity to consider comparability protocols?
  - Interesting new text in final guidance:

    "The proposed validation protocol is acceptable, but data could be requested."
  - Other protocols where data are not required are equipment cleaning, new product introductions (NPIs), cell banking
- Should movement within established design space require L3 reporting?
  - Working within the design space is not considered as a change - document with requisite change controls.

Where we had queries……

- If it's not a data requirement in an NDS should it be required in a change submission?
  - Examples:
    - Environmental monitoring data – trending/state of control is GMP – Remains a supporting data requirement
    - Laboratory qualification – Tech transfer is an NC
    - Water systems – now noted in diluent section
- If we think it's an Annual Notification and we get it wrong, what happens?
  - Supportive data can be sent on request – response time lengthened from 15 to 30 days, with clear guidance that sponsor may continue to distribute until resolution

A Few Specific Experiences…

- Numerous sponsors noted it's still early and there was still limited sponsor experience with the guidance
- General experiences are very favourable
- Vaccines colleagues have noted:
  - A trend towards requesting more accelerated stability data - may require changes to programs
  - Some missed targets for NCs – may reflect H1N1 workload
- Feedback on not bundling – may introduce challenges when global colleagues have combined changes
- Change from draft 2 that requires NCs for test transfers will require some backtracking

The Establishment License Challenge

- Consider the statements:
  A. Evidence that the new company/facility is GMP compliant.
  B. Confirmation that the proposed manufacturing site is listed on the Canadian Establishment Licence of the sponsor/manufacturer and/or confirmation of a satisfactory GMP rating by the Inspectorate.

Does A = B?

- There was little industry comment from statement A during the consultation period because A was not equated to the final statement B.

The Establishment License Challenge

- Challenges lie in facilities new to commercial production
- Inconsistent with other regulators
- Foreign inspections not available until after review begins
- OSEs don’t count
- The Inspectorate:
  - Has no published review targets – submission planning/timing very difficult
  - Is not resourced to conduct foreign inspections (most biologics)
  - Does not have extensive experience with biologics drug substance facilities

In Summary

- Experience is still limited
- The creation of one comprehensive guidance has been favourable
- The risk-based approach has generally been maintained through the drafts to the final version
- Late changes to the guidance linkage with Establishment Licensing requirements has created unexpected hurdles – and a first priority in the lifecycle management of this guidance

Thank You!