# Challenges with the QOS-CE CTA Industry View

October 7, 2008

*Canada's Research-Based Pharmaceutical Companies* (Rx&D)

Yannie Meletopoulos, CMC Project Leader, GlaxoSmithKline Inc.
Lisa Chartrand, Project Manager-Regulatory Affairs, Hoffmann La-Roche Ltd.

# Agenda

- Background
- Past Quality Issues
- How Revised Guidance Addresses Past Issues
- Outstanding Quality Issues
- Conclusions & Next Steps

# Background

- 2001-Health Canada introduced a new Clinical Trial Framework to facilitate a rapid and efficient process for preparation, review and approval of Clinical Trial Applications (CTA's)
- This new framework resulted in a decrease in review time and issuance of guidances and templates.
- Industry gained considerable experience in the use of the guidance/templates over the years.
- Based on this experience and the global nature of clinical trials, Industry identified an opportunity to better harmonize Health Canada requirements with other major agencies with respect to the Quality Requirements at early phases of clinical development (Phase I & II).

# Introduction (cont'd)

- Rx&D position paper (November 2005)
- Starting in 2006, representatives from Rx&D member companies met with HC to discuss greater harmonization of requirements with other major agencies (EMEA and the FDA).
- April 7, 2008: TPD issued draft Quality Guidance and draft QOS-CE templates for each phase of development

# Past Quality Issues

- Specification
  - Requests to tighten individual and total impurities in drug substance (DS) and drug product (DP) during early phase of clinical development (Phase I and II)
- Batch Analysis
  - Requests to provide batch analysis or Certificates of Analysis (C of A's) for each batch of DS and DP to be used in the clinical study.
- Method of Manufacture
  - Requests for detailed information on the method of manufacture of the DS and DP (Phase II)

# How Revised Guidance Addresses Past Issues

- Specification
  - Expansion of impurity batch tables (S.3.2) to include batch experience from a variety of batches (including toxicology, PK, etc.) that provide support to establishing impurity limits.
  - Placeholder for a brief justification of specifications (S.4.5, P.5.6) allows for opportunity to defend acceptance criteria using manufacturing experience, stability, historical batch analysis results and safety considerations.
  - Revised guidance acknowledges for Phase II that "Specifications are considered interim as they are based on a limited number of development batches. A higher degree of flexibility will be allowed in specifications with sufficient scientific justification.

# How Revised Guidance Addresses Past Issues

- Batch Analysis
  - Phase I, II: If C of A/Batch Analysis data is not available at time of filing, a commitment to submit them prior to study start is acceptable
  - Phase III: Representative batch analysis data considered acceptable
- Method of Manufacture
  - Phase II, DS: Flexibility afforded in the amount of detail required for describing the drug substance synthetic route allows for continued process optimization to occur.
  - Phase II, DP: No requirement to provide detailed process summaries-with the exception of sieve/screen size for immediate-release solid oral dosage forms.

# Outstanding Quality Issues

- Level of detail required for the following sections of Phase III approach the requirements at the NDS stage.
  - Controls of Materials (S.2.3)
  - Controls of Critical Steps and Intermediates (S.2.4, +P.3.4)
  - Pharmaceutical Development (P.2)
  - Validation of Analytical Procedures (S.4.3 + P.5.3)
- C of A/Batch Analysis Data for actual DS/DP lots to be used in the study

# Controls of Materials

- Revised draft guidance proposes that a specification be in place for starting materials at phase II and III.

---

- Industry has commented that the requirements at each phase be differentiated, and has proposed the following:
  - Phase II-Provide a high level overview of control being applied
  - Phase III-Provide provisional specs and limits being applied, recognizing that full specifications will be in place by the time of NDS.

# Controls of Critical Steps and Intermediates

- Revised draft guidance proposes that tests and acceptance criteria should be provided for controls on the critical steps for Phase III.

---

- Industry has commented that at Phase III, optimization is still ongoing and control strategy will still be under development.
- At this phase it would be appropriate to provide provisional key process controls and limits being applied, recognizing that discussion of control will be in place by the time of NDS.

# Pharmaceutical Development

- Considerably more detail seems to be requested at phase III
  - i.e. *The selection and optimisation of the manufacturing process described in P.3.3, in particular its critical aspects should be explained.*

---

- At Phase III, optimization is still ongoing and control strategy will still be under development.
- Rather, a summary of the evolution of the process should be provided explaining relevant changes in the context of the material intended for the clinical study.

# Validation of Analytical Methods

- Statement in draft guidance document "Methods should be fully validated by phase III " is not clear.

---

- An analytical method should be validated to a standard appropriate to assure it is fit for use for the phase of development.
- Validation to full ICH Q2 should only be required at the NDS stage.

# Batch Analysis

- C of A/Batch Analysis Data for actual DS/DP lots to be used in the study is still a requirement at Phase I and II.

---

- Requirement not consistent with EMEA and FDA requirements
- No additional benefit to Canadian patients, given that all batches to the clinic are released in accordance with the approved specifications.
- Therefore, representative batch analysis should be acceptable for all stages of clinical development.

# Conclusions & Next Steps

- New guidance provides distinct requirements for each phase.
- For Phase II, revisions to the guidance provide for a more harmonized approach with the requirements of other major agencies.
- However, level of detail required for Phase III approach level of detail required at NDS stage.
- Continued dialogue between Industry and TPD as the guidelines and template are finalized