Overview of Industry Submission Review Challenges

CAPRA – Streamlining Our Regulatory Process – Your Turn to Speak.

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navigating regulatory affairs

Natural Health Products

- How many people received their vitamin supplement when they checked in at the Westin?
  - Did you check it for NPN Number?
- The backlog is the issue at NHPD.
- Recent launch of a product that had been intended to be a prescription drug, launched as a NHP without a NPN number.
  - This is the norm.

Communication

- Meetings
  - Pre CTA
  - End of Phase II
  - Pre NDS
- What can you learn
  - Probable reviewer, and whether they have preferences in data presentation or format.
  - Whether there are internal “guidances” or “expectations” regarding this class of compounds.
  - Whether there were problems with this class of compounds in the past which will be a special area of interest for them with your compound.
  - Whether there is a problem lurking in your data that you are unaware of.

Guidances

- New Guidances that become available after your clinical program is done or while your NDS is in review.
  - E.g., *H. pylori* Guidance that went through several drafts before a final one was published.
    - Clinical studies are done to earlier draft requirement.
    - Newly published draft has different requirements.
- An example from the FDA for a new dosage form for chronic pain of a known compound
  - You need 2 phase III studies
  - No, for a chronic pain indication you need 2 phase III studies in 3 different pain models.
  - No, for a chronic pain indication you need 1 phase III study in any model

An Answer in the US

- Special Protocol Assessments
  - You submit your protocol and ask for a special protocol assessment
  - Once approved, the protocol is a contractual agreement between the regulatory agency and the company that the product will be approved if the primary results are positive.
  - Can be overturned if in the public health interest.

Internal Guidances That Are Not Public

- Internal Guidances
  - On occasion, there are internal guidances, that may not be published on the website.
    - For example, there are (or at least have been) internal guidances on submission of omeprazole products.
    - There are also guidances on submission of combination products and the need for studies with Latin Square designs.

Need for Canadian Importer/Distributor Before Filing

- TPD will not accept an NDS unless you identify the Canadian Importer/Distributor
  - Why isn't there consistent policy across Health Canada?
  - Why????
  - Forces companies to delay submissions or find an artificial way around this requirement.

Need for Canadian Company Holding DIN to Have Distributor EL

- When Is Health Canada going to tell us about this requirement???
- Multiple problems arise when one Canadian company owns the DIN and another distributes.
- We could work with Health Canada to avoid the problem – BUT WE NEED TO KNOW THE RULES FIRST.

Changes in Formulation

- Changes to formulation from clinical to market
  - E.g., clinical studies are done with a round, white tablet. Marketed supplies will have a different source of drug substance, a different drug product manufacturer, the tablet will be caplet shaped, there will be an imprint on the tablet and it will have a film coating.
  - Although each change taken on its own would not require bioequivalence, the formulation creep involved in the multiple changes would require that a bioequivalence study be done.

Validation Requirements for Bioassay

- Validation requirements for a bio-assay
  - Some bioassays have a very narrow concentration over which a very large biologic effect occurs.
  - Validation requires looking carefully at the linear portion of the curve for the assay.
  - Not understanding what BGTD will require has led to refusals to approve biologic products.
- This could be overcome with appropriate communication with Health Canada.

On Site Evaluation

- Common findings
  - Potential for cross-contamination or mix-up not adequately addressed
  - Inadequate process validation (either initial or to support modifications to the process)
  - For aseptically filled products, inadequate control over operations inadequate environment/utensils for dispensing formulation ingredients.
  - Media Fill Issues: Inappropriate invalidation of media fill
  - Inadequate control over reprocessing.
  - Calibration not present or not at an appropriate tolerance
- These are common issues that have little to do with the fact that the product is a biologic.

Post Approval - Lot Release Program

- Group 2 – Post-Approval – Sample Testing and Protocol Review
  - Products requiring the highest level of assessment after NOC
  - Targeted Testing
  - A formal Release Letter which approves the sale of the lot in Canada is required
  - Generally 6 weeks to release after receipt by Health Canada
- How much post-approval testing results in a different outcome than that from the company?

Preclinical

- Maximum Tolerated Dose (MTD)
  - Problems frequently arise with chronic toxicity data or carcinogenicity data where a multiple of the human dose has been used instead of the MTD.
    - Although ICH allows this, when there is any perceived positive tox signal, the study will likely have to be repeated using the MTD.
  - This can be avoided by using the MTD in the studies in the first place.
  - There is a newly released guideline on this from ICH, but the issue of when MTD can and cannot be used is still unresolved.

Preclinical

- When can you summarize from the literature or not
  - When genericized?
  - When patent runs out?
  - When there is lots of literature?

Non-Canadian Reference Drug

- When can a non-Canadian Reference Drug be used?
- What is the Canadian Reference drug?
- What generic products are approved without a Canadian reference drug?
- What is Health Canada requiring from generic companies for a given drug? If you ask (the right person), you might get an answer.

Statistics

- Per Protocol/ITT/Modified ITT differences
- How is missing data handled (LOCF, BOCF)?
- Should the confidence interval be 90% or 95% (or 97.5%)?
- Issues of this nature have prevented products from being approved in the past.

Statistics

- Modifying the Analysis from the one planned prospectively.
  - Modifying the Statistical Analysis after the study has been done is very difficult.
- Trying to use a secondary endpoint as a primary

Efficacy – Clinical Significance

- Statistical significance, there is a need for clinical significance in a study.
  - E.g., what value if an anti-cancer drug improves life expectation by 50%, I.e., from 6 to 9 weeks.
  - E.g., what value is Quality of Life, especially from an unvalidated scale.
- Better guidelines in terms of what Health Canada is expecting, especially for cancer studies, would be helpful.
  - E.g., when are biomarkers acceptable?

Efficacy – Phase 3

- Need for one or two Phase 3 studies
  - Consider an SR formulation of an existing compound
  - Do you need one or two Phase 3 studies
  - Does it vary depending if you own the IR product
- We need the equivalent of a 505(b)(2)

Clinical – Safety

- Long Term Safety
  - ICH defines long term safety requirements as 300-600 patients for 6 months, 100 for 12 months and 1500 exposed.
  - Not providing this required long term data is frequently a reason for refusing a submission.
  - In the Post Vioxx days, these requirements are really the minimum requirements.
- We need to find a better way to define this.

Clinical - Safety

- Issues Develop Post-Marketing in Another Country
  - E.g., Antidepressants and suicide
  - This postmarketing issue will cause Health Canada to screen all of the data in the NDS very carefully, probably asking for additional data, alternative coding of ADRs, explanations of specific ADRs and patients.

Clinical - Safety

- Issues with a Related Compound in the Class
  - E.g., Cisapride and QTc prolongation
  - This issue will cause any agent slowing motility to be very carefully reviewed.
  - Very specific studies related to this issue will need to be a part of any data package.

Labelling

- Mandatory use of Part III of the Monograph as a patient insert.
- Assumption that somehow industry can fix the issue of pharmacy chains giving out incorrect patient information.

Summary

- Issues that cause problems with submissions speak to a different understanding from industry versus what Health Canada is expecting.
  - Meetings
  - Guidelines
  - Standards
  - Database of Canadian Reference Product (could be handled within the Drug Product Database)