Health Canada Santé Canada

Canada

Regulatory Considerations for Excipients - Case Studies

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Overview

- Health Canada review of excipients in drug products
  - Equivalency to the safety and efficacy lots
  - Assessment of excipients
- Case studies
  - Ophthalmic sterile solution
  - Extended-release sterile solution
  - Extended-release tablet
  - Pediatric oral solution
  - Oral solution
- Conclusion
- Questions

Why does Health Canada care about excipient changes

- For innovative drugs: equivalent to the clinical lots
  - Subsequent commercial lots need to be reflective of the clinical lot in order to ensure that the safety and efficacy observed in the clinical lots is retained in the commercial lots

- For generic drugs: pharmaceutical equivalent and bioequivalent to the Canadian Reference Product (CRP)
  - Subsequent commercial lots need to be reflective of the lot used in the bioequivalence studies (biolot) in order to ensure that the efficacy observed in the bioequivalence studies (and safety of the CRP) is retained in the commercial lots

- Formulation changes that would affect the bioavailability of the drug product could potentially render the commercial lot unrepresented by the clinical/biostudy.

Health Canada: Assessment of Excipients

- For immediate-release products, the excipient grades are not typically considered critical, unless development studies demonstrated that specific grades were required for desired drug product performance.
- For modified-release tablets, excipients used in enteric coatings or to control the release are scrutinized.
- For ophthalmic solutions, excipient grades and specifications are verified for properties that can affect drug product performance (e.g. viscosity).
- Excipient functionality and physiochemical properties are critical for inhalation product performance.
- Nasal and topical products are treated on a case-by-case basis depending on the complexity of the product.

General excipient examples

- Hydroxypropyl cellulose has grades with different particle sizes and substitution levels
- Crospovidone particle size can influence disintegration and dissolution rate
- Lactose monohydrate particle size or flow characteristics may be required for manufacturing process
- Polyethylene glycol grades have different viscosity properties

Health Canada: Assessment of Excipients

- During review, developmental studies (3.2.P.2) are assessed to determine if studies were done on different excipient grades or properties. The drug product manufacturer should have a thorough understanding of the qualities required from critical excipients. Developmental data at the extremes of the proposed ranges for the critical parameter will be assessed to support the specifications.
- If specific grades or properties are required, the excipient specifications will be reviewed in detail.
- The formulation of the (proposed) commercial batches are compared to the biolot or pilot lots. The Master Production Documents (MPD) and Executed Batch Records (EBR) are often used for the comparative analysis. The specific grades required (for critical excipients) should be specified in the documents.

Health Canada: Assessment of Excipients

- If differences are noted, multiple strategies to resolve the issue can be employed, often concurrently:
  - Comments may be sent to the Sponsor to justify the differences.
  - A consult can be sent to the clinical division to determine whether the differing characteristics are clinically relevant.
  - Where available, information from products approved by another regulatory agency can be used to support the formulation changes.
  - Teleconferences can be held with the company.

- The next few slides show case studies where the above strategies have been used. Information on specific case studies has been changed and is not reflective of actual products assessed.

Eyedrops: General information

- Corneal epithelial absorption is most common
- Relatively brief contact time has to be considered
- Contact time can be enhanced with viscosity-imparting polymers
- Blurring, eyelash residue can occur at higher ends
- Need a relatively low viscosity to be dispensed from the container

Eyedrops: Viscosity of Excipient X

- Viscosity in clinical batch (3000 mPa at $7s^{-1}$) was different than commercial batches (2200-2400 mPa at $7s^{-1}$)
- Proposed viscosity range for the drug product was 2000-5000 mPa at $7s^{-1}$
- Different clinical formulations with varying levels of Viscosity Agent X
- Commercial formulation was the same as pivotal batch
- Different autoclave parameters during the steam sterilization of the viscous excipient solution resulted in a drop in viscosity for the commercial batches
- Lots of Excipient X could have different viscosity values at release

There was a concern as to whether the differences in viscosity between the commercial and clinical lots would impact residence time in the cornea (and consequently the extrapolation of the clinical study).

What data would have been needed:

- Additional clinical or animal studies where the proposed viscosity range was studied to demonstrate the absence of impact on clinical effectiveness.
- Information from clinical batches from product approved in other regulatory jurisdictions.

Proposed range (mPa at $7s^{-1}$)	Canadian pivotal clinical lot (mPa at $7s^{-1}$)	Canadian commercial (mPa at $7s^{-1}$)	EU commercial lots and accepted limit (mPa at $7s^{-1}$)
2000-5000	3000	2200-2400	2100-3100 Viscosity limit: 2000-5000

BPS recommendations:

Proposed range (mPa at $7s^{-1}$)	Canadian pivotal clinical lot (mPa at $7s^{-1}$)	Canadian commercial (mPa at $7s^{-1}$)	EU commercial (mPa at $7s^{-1}$)
2000-5000	3000	2200-2400	2100-3200 Viscosity limit: 2000-5000

a) Excipient concentration in animal studies should have same concentration of critical excipient as the pivotal study in order to be considered (3% versus 5%).

b) Ph. Eur. for Excipient X states that apparent viscosities should be 75-150% of the label's value. Mean viscosity from EU batches was 2690 mPa at $7s^{-1}$ therefore a range of 2018-4035 mPa at $7s^{-1}$ is acceptable for the Canadian product.

c) Proposed viscosity limit of 2000-5000 mPa at $7s^{-1}$ would be acceptable based on European product approval. The higher upper viscosity limits would be expected to produce exposures similar to clinical effectiveness studies provided.

Extended-release solution (two strengths)

- Commercial lots formulation were reflective of clinical lots.
- Molecular weight acceptance criteria in drug product (correlated to the MW of Excipient X) didn't correspond to MW in clinical batches.
- Excipient X is the rate-controlling polymer. Release rate is inversely proportional to the polymer's MW.
- Extreme ends of MW range (8 and 17 kDa) in bioequivalency studies did not meet TPD bioequivalence standards to the comparator lot (14 kDa).

Pivotal efficacy and safety lots	Proposed range	HC suggested range
Efficacy:11-16 kDa (lower) 12-16 kDa (higher) Safety: 11-15 kDa (lower) 12-17 kDa(higher)	8-17 kDa	12-16 kDa

What data would have been needed:

- Since there is an effect of MW on release, its range and control is more concerning. Safety and efficacy studies over the MW range proposed would be required.
- Studies supporting the molecular weight (MW) ranges of Excipient X and difference in pK profile. The studies should demonstrate the absence of meaningful differences in safety and efficacy of the drug product.
- Communications from other regulatory agencies regarding the MW specifications.

BPS recommendations:

- Lower dose with high MW polymer has efficacy concerns (slower release). Efficacy tested ≤16 kDa. Higher dose with low MW polymer has safety concerns (rapid release). Safety was only tested ≥12 kDa.

Pivotal efficacy and safety lots	Proposed range/Health Canada proposed	FDA	Revised range (shelf-life)
E: 11-16 kDa (L) 12-16 kDa (H) S: 11-15 kDa (L) 12-17 kDa(H)	8-17 kDa/ 12-16 kDa	8-16 kDa (17 kDa not acceptable)	8-16 kDa (L) 12-17 kDa (H)

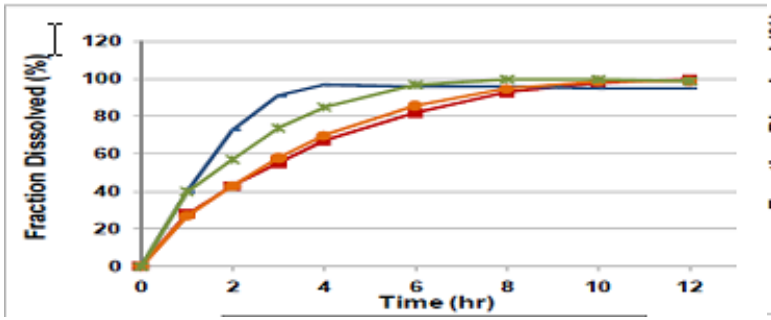
- Specifications for Excipient X considered CQA and any change in the polymer, supplier, manufacture would be considered a significant change and would need supplement.
- Excipient commercial name and grade clearly indicated in MPD.
- Raw material specifications tightened.

E= Efficacy S= Safety
L= Lower strength H= Higher strength

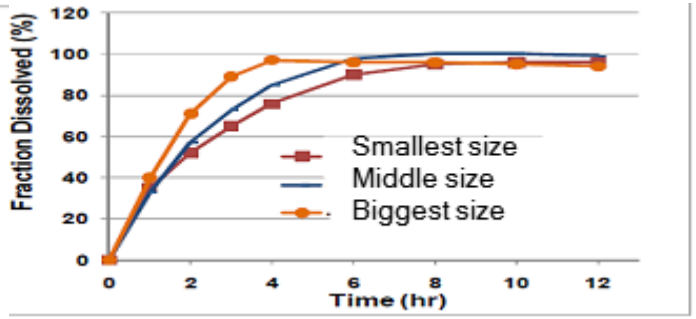
Extended-release tablets

- Biostudies were performed on lowest and highest strengths. IVIVC was available to support intermediate strengths which were dose proportional to the highest strength.
- Substituent concentration and distribution range of particle sizes were different between lower strengths and the highest strength.
- Variability in substituent content and PSD for Excipient X directly affects the release.

Variability in % substituent content



Variability in PSD (d90)



Extended-release tablets

- Example of specifications for an excipient where the variability in polymer side chain content and PSD directly affects the release:

	Substituent Content	Specification	D(50) µm	D(90) µm
Lowest strength	59.9	58-62	29.9	98.0
Highest strength	56.7	55-58	70.4	213.2
Proposed single specifications		55-62	15-80	230

- Are the single specifications adequate to ensure the drug product performance, regardless of tablet strength, is reflective of the bioequivalence lots?

What data would have been needed:

- Dissolution data or statistical analysis with varying substituent content to support the proposed limit of 55.0-62.0% or tighten the specifications.
- Particle size distribution specifications, in a three-tiered style, based on the lots used in bioequivalence studies.
- Additional batch data with extensive statistical analysis supporting the specification range for substituent content and PSD could be provided. PSD should be controlled in three-tiered approach.

<u>BPS recommendations:</u>

Due to the critical nature of the excipient's attributes, we recommend:

- Qualified supplier for Excipient X
- Specifications for Excipient X should include supplier name and specific product code
- Supplier name and code for Excipient X should be included in MPD

Oral Solution: Impurity limits in excipient

- Many products develop an oral solution as a product-line extension to immediate-release tablets.
- Target population: pediatric patients and geriatrics (in which swallowing is difficult or compromised)
- Glycerol is often the main component in the formulation
  - A common pharmaceutical excipient (e.g., palatable syrups)
  - Used in many manufacturing sectors / applications, including:
    - Cosmetics (ingredient or processing aid)
    - Toiletries
    - Personal care products
    - Medicines / pharmaceuticals
    - Foodstuffs
    - Precursor to polyols for flexible foams)
  - *Glycerol in commercial applications controlled as per stringent requirements of USP and FCC (Food Chemicals Codex)*

Oral Solution: Impurity concerns

- What represents a safe exposure to pediatric population? Is it appropriate to apply the standard USP, Ph. Eur. limits for potentially harmful impurities (NMT 0.10% for ethylene glycol and diethylene glycol)?
- Would this result in a greater health hazard for pediatric patients based on the dosage regimen and duration of treatment?
- If tighter limits for these impurities need to be applied, what limits would be appropriate?

BPS recommendations:

- Although diethylene glycol (DEG) is less toxic than ethylene glycol (EG), a conservative approach would be needed based on the intended population. The same permitted daily exposure (PDE) would be applied to both impurities.
- PDE for ethylene glycol in ICH Q3C guideline (R7) is 3.1 mg/day.
- Tighter limit than that specified in compendial monographs should be applied.
- The specification for glycerol should comply with the Ph. Eur. monograph and included tighter controls on the levels of EG and DEG. The allowable concentrations should correspond with a maximum daily exposure for each impurity of 3.1 mg/day in accordance with ICH Q3C(R7).

Oral Solution Case Study: Flavouring agents

- Formulations may contain proprietary flavouring mixture.
- Insufficient information provided in the submission regarding the qualitative composition:
  - Attested that major components (carriers) were “food grade”
  - The flavouring ingredients not identified but referred to as “flavouring preparations, natural flavouring substances”
  - Justification for lack of data and MF was that the ingredients are “food grade”.
- Requirements of Food and Drug Regulations that a list of the ingredients needs to be provided.

BPS recommendations:

- Technical data sheet for the flavouring agent in lieu of a Master File is unacceptable.
- Flavouring agents require review. Proprietary information in quantitative composition can be disclosed by way of a Master File.
- Essential to know what the flavouring agent is comprised of since the acceptability of ingredients may evolve over time.

In conclusion:

- Excipient grades and properties can impact the pharmaceutical equivalence of a drug product.
- Health Canada will consider data provided by the Sponsor and available information from international regulatory agencies when examining the effect of excipients and any additional controls required.
- BPS works together with the clinical and bioequivalence divisions to assess the acceptability of the data provided.
- Controls can vary depending on the concern and product.

References and Useful Documents

- Handbook of Pharmaceutical Excipients
- Remington: The Science and Practice of Pharmacy 21st ed
- Quality (Chemistry and Manufacturing) Guidance: New Drug Submissions (NDSs) and Abbreviated New Drug Submissions (ANDSs)
- Post-Notice of Compliance (NOC) Changes: Quality Guidance