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Bioequivalence Standards for Multiphasic Modified- Release Drug Products

Canadian Society for Pharmaceutical Sciences

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Outline

- Scientific Advisory Panel – Bioequivalence Requirements for Modified Release Dosage Forms
- 2017 Notice to Stakeholders
- Stakeholder Comments on Notice
- Final Guidance 2018

Multiphasic Modified Release Dosage Form

- Formulations designed to provide, after single administration, multiple peaks and troughs in the concentration-time curves (e.g. deliver a rapid onset action followed by a sustained release).

- Can be a combination of immediate release, delayed release, and extended release components within the same product.

- Can occur in a variety of formulations.

Scientific Advisory Panel - 2010

- The introduction of multiphasic modified release products and the development of subsequent entry products using the drugs as the Canadian Reference Product led Health Canada to determine whether BE requirements were sufficient.

- In 2010, Health Canada convened a Scientific Advisory Panel on Bioequivalence Requirements for Modified Release Dosage Forms.

- Two key questions were put before the panel
  - Were the current comparative bioavailability metrics and standards adequate for modified release dosage forms?
  - If current metrics and standards are considered inadequate what metrics and standards would be recommended and under what circumstances would they be applied?

- The format of the meeting allowed for direct stakeholder involvement to allow for greater transparency in policy development.
  - Presentations provided by government, industry, and academia

Scientific Advisory Panel Recommendations

Presentations were made to the SAP specific to multiphasic release products and the deliberations by the SAP took these into consideration when making the following recommendations.

Were the current comparative bioavailability metrics and standards adequate for modified release dosage forms?

The current comparative metrics and standards are adequate, with rare exceptions, such as time sensitivity of drug release to elicit a therapeutically significant outcome.

The evidence to support exceptions must be in the product monograph of the original product and changes in rate of drug delivery throughout the day must be reconciled with matching generally accepted and clinically relevant response data generated from a well designed randomized clinical trial program

If current metrics and standards are considered inadequate what metrics and standards would be recommended and under what circumstances would they be applied?

For the rare exceptions possible, the metrics and standards would need to be addressed on a case by case basis.

Notice of Proposed Modifications to Guidance

In July, 2017 Health Canada published a notice with proposed modifications to the bioequivalence standards for multiphasic modified-release drug products.

•Modified-release products with multiphasic plasma concentration profiles demonstrated to be integral to their therapeutic effect will be subject to standards on the partial area under the concentration versus time curve (pAUC), defined over a restricted time interval(s) after drug administration. These standards will be applied in addition to those normally applied in the assessment of bioequivalence (i.e. AUC and C_{max}). Specifically, standards based on the 90% confidence interval of pAUC metrics should be met.

•The requirement for pAUC assessment metrics for multiphasic modified-release formulations will be based on data available from various sources, including but not limited to peer-reviewed scientific literature and the approved Canadian labelling, as applicable.

•The time course of changes in the rate of drug delivery throughout the day should be reconciled with generally accepted and clinically relevant response data generated from a well-designed randomized clinical trial program.

•The specific pAUC time intervals to be considered will be based on clinical data showing the therapeutic relevance of the particular time interval (e.g. early onset, maintenance, dose clearance, fasted versus fed state). Selected time intervals should be justified, specified a priori and applied to all study subjects for both the test and reference products.

Stakeholder Response to Notice

Over 30 comments received from stakeholders (Industry, Association, Healthcare providers)

Key Issues:

- Proposed requirements should apply to products beyond solid oral products (IM, SC, Transdermals)

- Data to determine application of the additional standards be broader than just RCTs

- Standards should be applied retroactively

- Clearly identify products that are subject to the new standards

Health Canada Response to Comments

- Proposed requirements should apply to products beyond solid oral products (IM, SC, Transdermals)
  - Given that the focus of the current guidance is solid oral dosage forms, inclusion of specific statements on injectables would require consultation beyond the scope of the current exercise.
  - However, should a product in a dosage form other than a solid oral have evidence demonstrating that the multiphasic profile was intergral to the therapeutic effect then application of the standard could be considered.

Health Canada Response to Comments

- Data to determine application of the additional standards should be broader than just RCTs

  – The proposed wording states “The requirement for pAUC assessment metrics for multiphasic modified-release formulations will be based on data available from various sources, including but not limited to peer-reviewed scientific literature and the approved Canadian labelling, as applicable.”

  – The data needs to be robust and clearly establish linkage between multiphasic profile and therapeutic effect.

Health Canada Response to Comments

- Standards should be applied retroactively
  - Where a safety or efficacy issue is seen, an approved product will need to be re-assessed.
  - To date there has not been an instance identified that would require reassessment of marketed products.

Health Canada Response to Comments

- Clearly identify products that are subject to the new standards

  – Health Canada will consider publishing names of reference products that necessitate standards on pAUC, when it is demonstrated that those products require special standards. Currently, appropriate data has not been provided for any products.

  – Companies are invited to ask Health Canada, prior to developing a product, whether standards on pAUC are expected to be applied for a particular product. It is anticipated that the innovator product's product monograph will contain sufficient information to prompt sponsors to make such enquiries.

Final Guidance Document

- The comments received from stakeholders did not alter the requirements proposed in the notice and the updated Guidance Document – Comparative Bioavailability Standards: Formulations Used for Systemic Effects was published in July, 2018.

- While this publication established clarity for both the innovative and generic pharmaceutical industry, it should be noted that these standards could have been applied if required prior to publication.

- Though specific to solid oral dosage forms could be applicable to other formats if warranted by the evidence.

- Where relevant, information will be included in Product Monograph. However, Health Canada can rely on additional sources of data to determine whether or not a requirement for pAUC assessment metrics is warranted.

THANK YOU!

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