Introduction to Permeability for BCS-Based Biowaivers

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Scope of BCS Biowaivers

Used to substantiate in vivo BE for comparison of products in the following situations:

- Comparison between products used during clinical development through commercialization
- Support of post-approval changes
- Generic drug products comparing to the innovator

BCS Biowaivers-Eligibility

Eligible

- Only for immediate release dosage forms designed to deliver drug to the systemic circulation
- Fixed-dose combination products may be eligible when all drug substances therein meet relevant BCS criteria
- Pro-drugs if absorbed as the pro-drug
- Test product containing different salt of the drug substance than the reference product may be eligible for a BCS I-based biowaiver depending on the context
- Test and reference must be the same dosage form and strength

Not Eligible

- Narrow therapeutic index drugs
- Drug products with buccal or sublingual absorption
- Test product contains a different ester, ether, isomer, mixture of isomers, complex, or derivative of the drug substance than the reference listed drug product

Evidence For BCS-based Biowaivers

BCS Class I-based biowaivers:

Highly permeable drug substance + Highly soluble drug substance + rapid and similar dissolution between T and R + acceptable excipients

BCS Class III-based biowaivers:

Highly soluble drug substance + Very rapid dissolution for T and R + qualitatively the same and quantitatively similar formulations between T and R

*It is noted that it is not necessary to demonstrate the permeability status of the API if pursuing a BCS Class III-based biowaiver. However, excipient effects on permeability and absorption of the API should be considered.

Permeability: Study Types/Evidence

- In vivo human pharmacokinetic studies
  - Absolute bioavailability, Mass balance
- Caco-2 cells
- Other methods (e.g., non- Caco-2 cell lines, ex vivo, in situ, in silico)
- Literature information

Mass Balance Studies: Considerations

- High permeability can be concluded if ≥ 85% of the administered dose is recovered in urine as unchanged drug or as the sum of Phase I oxidative and Phase 2 conjugative metabolites

- Metabolites in feces can be considered as reflective of parent drug absorption if oxidative or conjugative.

- Unchanged drug in feces can be considered as reflective of parent drug absorption if it can be demonstrated that the drug was absorbed and then excreted or secreted back into the GI tract or that the drug is present due to an unstable metabolite.

- Reduced or hydrolyzed metabolites can be considered as reflective of parent drug absorption if it can be demonstrated that they were not formed prior to absorption

- GI tract stability for the drug substance must be demonstrated if using a mass balance approach to demonstrate high permeability.

Caco-2 Studies: Considerations

- Limited to drugs that are passively transported through this cell line. Passive transport should be demonstrated for the test compound in cells that express efflux transporters.
- Validation should be performed using model drugs to demonstrate that the experimental system can differentiate between drugs of differing permeability.
- Model drug permeability standards should be dosed with the test drug substance.
- The test drug is considered highly permeable when its permeability value is greater than or equal to the selected high permeability standard.
- GI tract stability for the drug substance must be demonstrated if using a mass balance approach to demonstrate high permeability.

Other Methods

- For example, cell lines other than Caco-2, ex vivo, in situ, in silico.
- Regulatory agencies only have limited experience with the above methods and thus at this time only in vivo or Caco-2 data are considered for permeability assessment.

Breakout Topic # 1: In Vitro and In Silico Permeability Methods.

Literature

- May be acceptable to support high permeability of the drug substance.
- However, information from the literature sources may not provide enough information or may be conducted in a manner inconsistent with being able to make a regulatory decision.

Breakout Session #3: Use of label and literature data to designate the permeability class

Excipients and Permeability

- In addition to demonstrating high permeability of the drug substance to support a BCS Class I waiver, it must be shown that excipient differences between the test and the reference formulations do not differentially affect absorption of the drug substance.

- Effects of excipient differences on intestinal permeability should be considered, for example interactions of excipient with intestinal drug uptake transporters.

- For BCS I-based biowaivers, excipients that affect absorption should be qualitatively the same and quantitatively similar between test and reference products (i.e., within ± 10% individually and cumulatively)

- Excipient differences and resultant effects on absorption are more of a concern for BCS Class III biowaivers: With the exception of film coating and capsule shell components, all of the excipients must be qualitatively the same and quantitatively similar between test and reference formulations.

Breakout Session #2: Excipient Effects on Permeability, Do We Need to be Concerned?

Summary

- High permeability may be demonstrated using a number of different approaches, but only Caco-2 and in vivo methods are considered at this time.
- Literature or label information could be used to substantiate high permeability in support of a BCS-based biowaiver, but there are caveats.
- Permeability of the drug substance is only one aspect of the BCS-based biowaiver; the effect of excipients on drug permeability and absorption should also be considered.

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