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Biopharmaceutics – BCS Biowaivers:

Generic Drug Industry's Perspectives on BCS-based Biowaiver

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Other Relevant Involvements

- Chair, Bioequivalence Committee of Canadian Generic Pharmaceutical Association
- Chair, Generic Pharmaceuticals Focus Group of American Association of Pharmaceutical Scientists
- Member of Bioequivalence Working Group, European Generic Medicines Association
- Lecturer (Status Only), Faculty of Pharmacy, University of Toronto

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Patients Need Affordable Medicines

- Generics significantly reduce cost of medicines but they need to perform just as well as the brand products
- Regulators have to ensure proper testing of generic drugs be done
- Significant saving can only be passed on to customers if generics are not over-burdened with unnecessary studies or requirements
- It is important for Regulators to foster this environment

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Requirements for Approval of Generic Drugs

- Main in vivo study requirements are single-dose fasted and/or fed comparative bioavailability (BA) studies to demonstrate bioequivalence (BE)
- In general, current BE methodology works well
  - 2-way crossover design allows within-subject comparison of products
  - Pharmacokinetic measures (eg. AUC & Cmax) provide adequate assessment of rate and extent of drug absorption
  - The 90% confidence interval requirement provides further assurance of “sameness” between brand & generic products

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BCS-Biowaiver Offers Significant Saving on Cost and Time

- For a typical BE study of 24-36 subjects:
  - Cost: $250,000
  - Time: 3 months
- Waiver of BE studies in ANDAs for BCS Class 1 drugs provides significant cost and time saving
- Also reduce unnecessary human exposure to drugs

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Misconception

- BCS Class 1 drugs should exhibit low variability in BA and thus, require small sample size for the BE studies
  - Potential cost saving may be low
- Tends to be true for AUC but not for Cmax
- Rapid dissolution followed by rapid absorption for Class I drugs could result in significant variability of Cmax
  - Difficulty in capturing a sharp peak of a PK profile
- Hence, moderate to large sample size may still be needed

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Benefit of Global Harmonization

- Apotex, like many generic companies, develops products for global marketplaces
- Further savings can be achieved if only need to meet one set of rules
- BCS-Biowaiver has been accepted by many regulatory authorities such as EU EMA and WHO
- Health Canada also published a Guidance on BCS-Biowaiver recently (2014)
  - Very similar to that of EMA
- No official guidance by Australian TGA but they tend to follow the EU Guidance

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Harmonization is Possible

- Requirements for BCS-biowaiver are similar among the major jurisdictions
- Recent revision of FDA BCS Guidance reduces the number of differences to that of other jurisdictions
  - A big step forward toward harmonization

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Notable Changes of FDA BCS Guidances

Significant changes include:

- Add biowaiver for BCS Class 3 drugs
- Permeability boundary from 90% to 85%
- pH solubility range from 1 - 7.5 to 1 - 6.8
- “Highest dose strength” to “highest strength”
- Dissolution media volume from 900 mL to 500 mL
- Clarification of requirements for Fixed Dose Combinations and Orally Disintegrating Tablets
- Strengthen GI stability requirements

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Critical Differences Between FDA and Others

Few differences in biowaiver criteria still exist:

- Highest single therapeutic dose vs highest strength for solubility determination
  - Clinical relevance vs BE testing relevance
    - Highest dose ensures BE with all clinically relevant doses
    - Highest strength is usually used in dissolution testing in support of biowaiver and in BE studies; thus, adequate in justifying biowaiver
    - No clear-cut answer but highest dose may be problematic to apply as therapeutic doses could be different among countries for some drugs

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Critical Differences Between FDA and Others – Cont'd

- Dissolution testing
  - Media volume: 500 mL vs 900 mL for both Apparatus 1 and 2
    - 900 mL is a common compendial volume
    - No clear reason for reducing the volume to 500 mL by FDA – any examples that show 900 mL being inadequate?
  - Paddle speed: 50 or 75 rpm for App. 2
    - EU requires 50 rpm while 75 rpm is acceptable to WHO
    - FDA allows 75 rpm if justified by evidence of rapid in vivo dissolution (e.g. similar BA with a simple aqueous solution for RLD)

Critical Differences Between FDA and Others – Cont'd

- GI Permeability Determination
  - Role of in vivo or in situ intestinal perfusion studies in animal or in vitro model
    - Accepted as pivotal data by FDA for passively transported drugs
    - Considered supportive evidence by others, probably due to concerns on their correlation to GI permeability in human

** Personal view: if proper validation and correlation have been demonstrated, there is no good reason not to accept them as pivotal

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In Vitro Model with Caco-2 Cells

Common in vitro permeation study: use of cultured monolayers of epithelial cells such as Caco-2 cell line

- Limited experience of using it for permeability assessment
- Cost of study:
  - 5,000 – 7,000 USD for a pilot/feasibility study
  - Upwards of 30,000 USD for pivotal study
- The cost can eat into the saving of biowaivers
  - May not be worthwhile for some Class 1 drugs (i.e. with very low PK variability)

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Apotex Experience with BCS-Biowaivers for ANDAs

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ANDA Status with BCS-Biowaiver

Status	Number	Option of BCS-biowaiver not specified by FDA *
Approved	5	2
Tentative approval	3	0
Pending approval	1	0
Under review	2	1

*Evidence for being considered Class 1 not readily available in labeling of RLD

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Lessons Learned

Mostly from early times when BCS-biowaiver was first allowed

Solubility issues:

- Replicate solubility data at different pHs
- Solubility method, its validation and details of date, time, testing site, etc. not in FDA recommended format
- Volume and composition of buffer solution used for solubility
- Raw and individual numerical data for the solution stability study
- Repeat testing using FDA recommended buffers

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Lessons Learned –Cont'd

Solubility issues:

- Provide a graphic representation of mean pH-solubility profile
- Document that in solubility experiments the drug substance is not degraded as a function of buffer composition and/or pH.
- Use of sonication during solubility evaluation instead of shake-flask method

Permeability issues:

- Conduct your own permeability studies as described in the BCS Guidance or utilize the information contained in the approved labeling of the reference product

Lessons Learned –Cont'd

Dissolution issues:

- Dissolution specs (release and stability) and media not acceptable
- Dissolution method, validations and details of date, time, testing site, etc. not in FDA recommended format
- Expiry and stability status of Test product and RLD

Other issues:

- Stability of API in GIT
- Justification for choosing simulated gastric and intestinal fluids without enzymes instead of human gastrointestinal (GI) fluids
- Comparison of degradation studies of RLD and Test product

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GI Permeability Determination

- Time and cost savings may not be worthwhile for some Class 1 drugs if in vitro permeation studies or in vivo/in situ intestinal perfusion studies are needed
- Great incentive to look for mass balance or absolute BA data via credible sources
- Previous experience indicates that FDA readily accepts information in the labeling of RLD
- May not be clear in the labeling but might have been considered Class 1 in the Summary Basis of Approval by NDA reviewer or in the literature

Should Non-Labeling Sources of Information be more acceptable?

- More ANDAs with BCS-biowaiver would occur if non-labeling source of mass balance or absolute BA data is readily accepted by FDA
  - Why can't the opinions of NDA reviewers or other researchers in the literature be more acceptable?
- Even more important to old drugs that do not have much PK data in the labeling or SBOA
  - Very low profit margin
  - ANDA may not be worthwhile if BE studies or permeation studies are needed

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BCS-Biowaiver of Class 3 Drugs

- Less impactful than Class 1 drugs because of the more restricted requirements on formulation composition
- May not be possible to have same excipients due to patent constraint
- Even if qualitative compliance is possible, would still require performing reverse engineering in order to be quantitatively very similar to the RLD
  - Not inexpensive to perform
- Should revisit the requirements when there is more experience accumulated by FDA

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Summary

- Significant time and cost savings for generic drug development have been achieved with BCS-biowaiver
  - Benefits can be passed on to patients
- Global harmonization provides further opportunities for more savings
  - Changes proposed in the revised FDA Guidance are significant step forward toward harmonization
- Still have room for improvement
  - Revisit guidance after accumulating more regulatory experience

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Thank you!

Questions?

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