Biopharmaceutics – BCS Biowaivers:
Generic Drug Industry's Perspectives on BCS-based Biowaver

Yu Chung Tsang, B.Sc. Phm, Ph.D
Chief Scientific Officer, Biopharmaceutics – Biostatistics, Scientific & Regulatory Affairs, Apotex
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
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
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
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
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
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
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
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
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
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
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)
Apotex Experience with BCS-Biowaivers for ANDAs
## ANDA Status with BCS-Biowaiver

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*Evidence for being considered Class 1 not readily available in labeling of RLD*
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
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
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
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
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
Thank you! Questions?